

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

BIOVAIL LABORATORIES INTERNATIONAL SRL )  
a corporation of Barbados, )  
 )  
Plaintiff, ) C.A. Nos. 05-586 (GMS)  
 ) 05-730 (GMS)  
v. ) 06-620 (GMS)  
 ) (CONSOLIDATED)  
ANDRX PHARMACEUTICALS, LLC and )  
ANDRX CORPORATION, ) **REDACTED -**  
 ) **PUBLIC VERSION**  
Defendants. )  
 )

**JOINT APPENDIX OF INTRINSIC AND EXTRINSIC EVIDENCE**  
**(VOLUME 1 OF 3)**

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**Biovail Laboratories International SRL v. Andrx Pharmaceuticals, LLC et al.  
U.S.D.C. Del. Case Nos. 05-586, 05-730, 06-620 (GMS) Consolidated**

**JOINT APPENDIX OF INTRINSIC AND EXTRINSIC EVIDENCE**

<b><u>Tab</u></b>	<b><u>Description</u></b>	<b><u>Party Citing</u></b>	<b><u>Page(s)</u></b>
1	U.S. Patent 5,529,791	Biovail  Andrx	A-1 – A-8
2	Amendment dated June 22, 1992	Biovail	A-9 – A-27
3	Deboeck declaration dated April 20, 1993	Andrx	A-28 – A-42
4	Amendment dated April 26, 1993	Biovail	A-43 – A-63
5	Amendment dated May 28, 1993	Biovail  Andrx	A-64 – A-83
6	Amendment dated December 14, 1995	Biovail  Andrx	A-84 – A-92
7	The American Heritage Dictionary of the English Language, p. 841 (4th ed. 2000)	Biovail	A-93 – A-95
8	Webster's Encyclopedic Unabridged Dictionary of the English Language, p. 447 (1989 Ed.)	Andrx	A-96 – A-98
9	Webster's Encyclopedic Unabridged Dictionary of the English Language, p. 680 (1989 Ed.)	Andrx	A-99 – A-101
10	Webster's Encyclopedic Unabridged Dictionary of the English Language, p. 865 (1989 Ed.)	Andrx	A-102 – A-104
11	Darrell D. Ebbing, General Chemistry, p. G-16 (3rd ed. 1990)	Andrx	A-105 – A-107
12	U.S. Patent 7,108,866	Biovail  Andrx	A-108 – A-143
13	Amendment dated May 3, 2001	Andrx	A-144 – A-265

<b><u>Tab</u></b>	<b><u>Description</u></b>	<b><u>Party Citing</u></b>	<b><u>Page(s)</u></b>
14	Amendment dated November 22, 2001	Andrx	A-266 – A-359
15	Amendment dated August 12, 2002	Andrx	A-360 – A-439
16	Amendment dated February 4, 2004	Biovail  Andrx	A-440 – A-497
17	Affidavit of Edith Mathiowitz with exhibits dated April 10, 2005	Biovail  Andrx	A-498 – A-750
18	<i>Guidance Oral Extended (Controlled) Release Dosage Forms In Vivo Bioequivalence and In Vitro Dissolution Testing</i> prepared under 21 CFR 10.90(b)(9) by Shrikant V. Dighe, Ph.D., Director, Division of Bioequivalence Office of Generic Drugs dated Sep. 3, 1993 and concurred by Roger L. Williams, M.D., Director, Office of Generic Drugs, Center for Drug Development Research dated Sep. 4, 1993.	Biovail  Andrx	A-751 – A-764
19	<i>Guidance Statistical Procedures for Bioequivalence Studies Using A Standard Two-Treatment Crossover Design</i> prepared under 21 CFR 10.90(b) by Mei-Ling Chem, Ph.D., Division of Bioequivalence Review Branch II dated June 12, 1992 and Rabindra Patnaik, Ph.D., Division of Bioequivalence Review Branch II dated June 26, 1992, approved by Shirkant V. Dighe, Ph.D., Director, Division of Bioequivalence dated June 29, 1992 and concurred by Roger L. Williams, M.D., Director, Office of Generic Drugs dated June 29, 1992	Biovail  Andrx	A-765 – A-777
20	United States Pharmacopiea No. XXIII and its supplements	Biovail  Andrx	A-778 – A-855
21	U.S. Patent 4,032,637	Biovail	A-856 – A-858
22	U.S. Patent 4,336,263	Biovail	A-859 – A-865

<b><u>Tab</u></b>	<b><u>Description</u></b>	<b><u>Party Citing</u></b>	<b><u>Page(s)</u></b>
23	U.S. Patent 4,018,933	Biovail	A-866 – A-873
24	<i>Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations</i> , U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) March 2003, Revision 1	Biovail	A-874 – A-899
25	Declaration of Professor Ronald Bodmeier, Ph.D. in Support of Andrx’s Answering Claim Construction Brief, dated April 24, 2007	Andrx	A-900 – A-969
26	Declaration of Sanford M. Bolton, Ph.D. in Support of Andrx Pharmaceuticals, LLC’s and Andrx Corporation’s Claim Construction	Andrx	A-970 – A-1035

# EXHIBIT 1



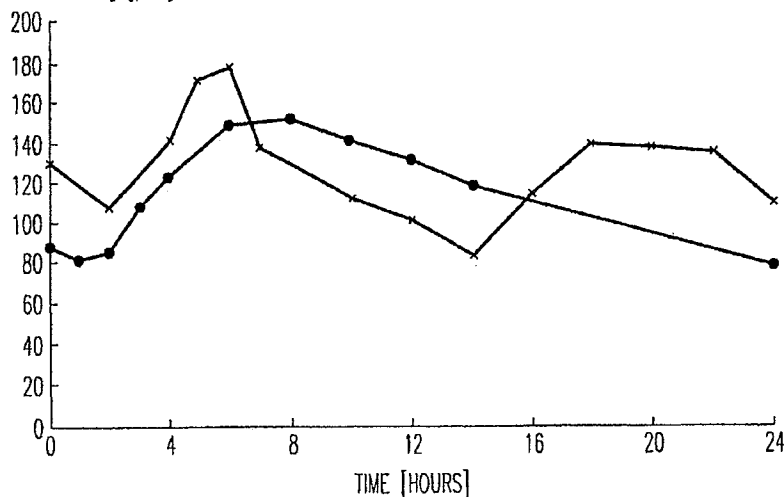
US005529791A

**United States Patent** [19]**Deboeck et al.**[11] **Patent Number:** **5,529,791**[45] **Date of Patent:** **Jun. 25, 1996**[54] **EXTENDED RELEASE FORM OF DILTIAZEM**[75] **Inventors:** Arthur M. Deboeck, Gurabo, Puerto Rico; Philippe R. Baudier, Waterloo, Belgium[73] **Assignee:** Galephar P.R., Inc., Ltd., Carolina, Puerto Rico[21] **Appl. No.:** 311,722[22] **Filed:** Sep. 23, 1994**Related U.S. Application Data**

[63] Continuation of Ser. No. 68,951, May 28, 1993, abandoned, which is a continuation of Ser. No. 721,396, Jun. 26, 1991, Pat. No. 5,288,505.

[51] **Int. Cl.<sup>5</sup>** ..... A61K 9/16; A61K 9/58; A61K 9/62[52] **U.S. Cl.** ..... 424/494; 424/490; 424/497; 514/777; 514/785; 514/786; 514/970[58] **Field of Search** ..... 424/457, 458, 424/462, 490, 493, 497, 498, 499, 494[56] **References Cited**  
**U.S. PATENT DOCUMENTS**5,112,621 5/1992 Stevens et al. .... 424/497  
5,275,824 1/1994 Carli et al. .... 424/490*Primary Examiner*—Thurman K. Page  
*Assistant Examiner*—James M. Spear  
*Attorney, Agent, or Firm*—Oblon, Spivak, McClelland, Maier & Neustadt[57] **ABSTRACT**

An extended-release galenical form of Diltiazem or a pharmaceutically acceptable salt thereof, which comprises beads containing said Diltiazem or a pharmaceutically acceptable salt thereof as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant.

**4 Claims, 2 Drawing Sheets****DILTIAZEM PLASMA [ng/ml]**

U.S. Patent

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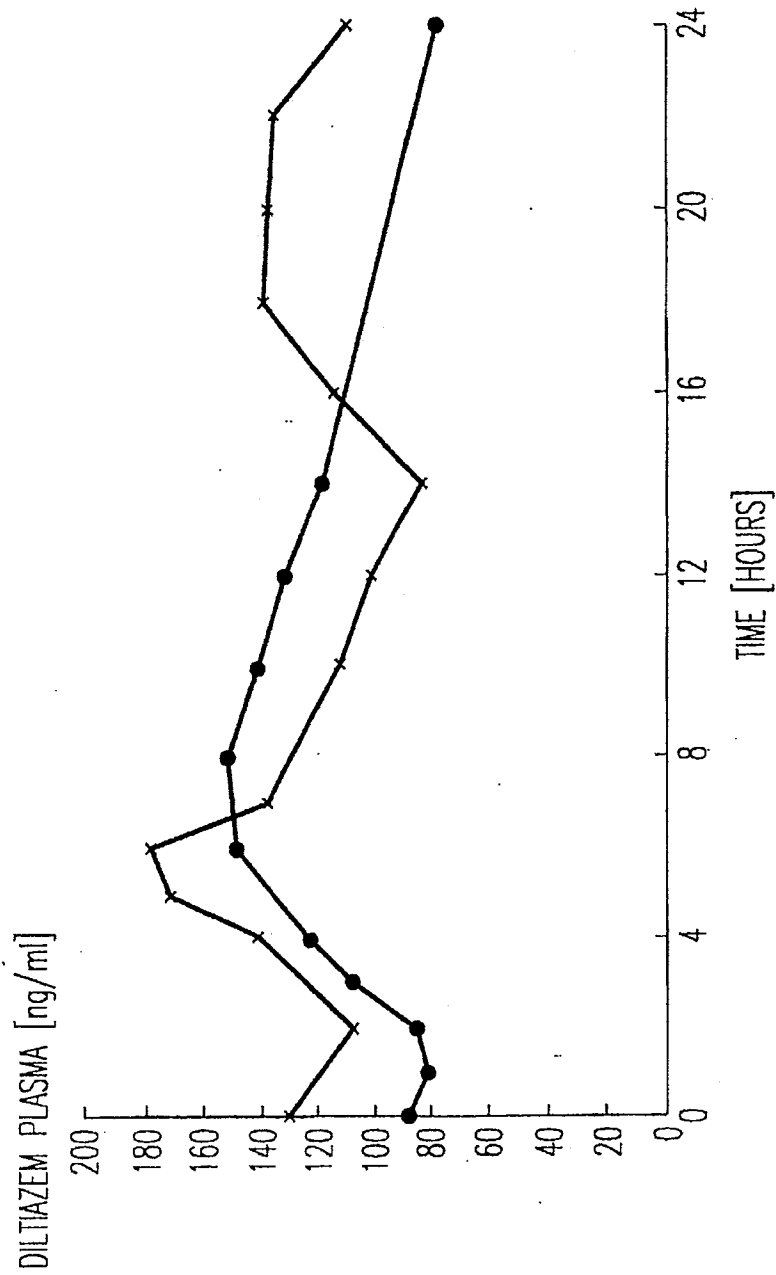


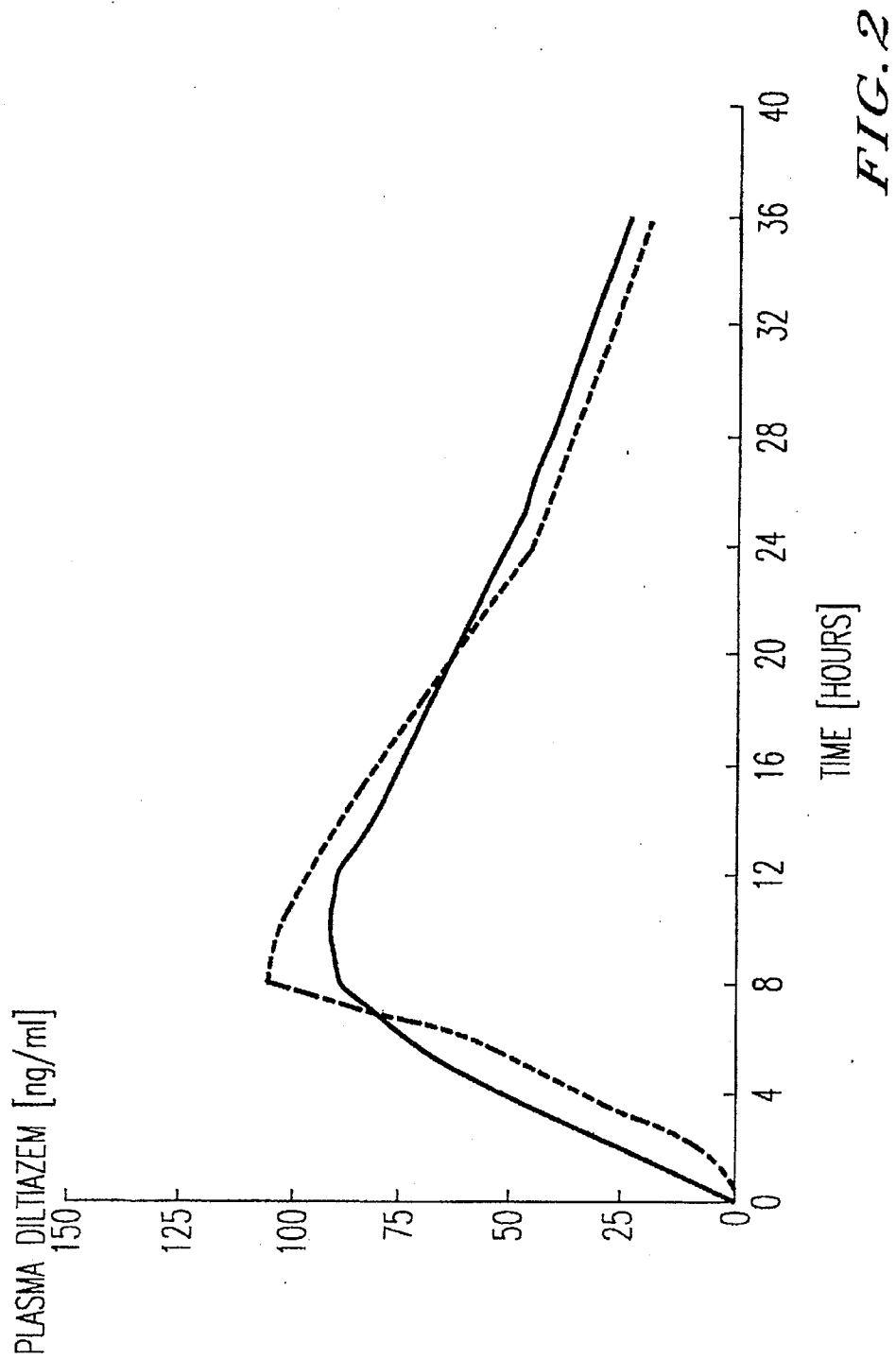
FIG. 1

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## EXTENDED RELEASE FORM OF DILTIAZEM

This application is a continuation of application Ser. No. 08/068,951, filed on May 28, 1993, now abandoned, which is a continuation of application Ser. No. 07/721,396 filed Jun. 26, 1991, now U.S. Pat. No. 5,288,505.

### BACKGROUND OF THE INVENTION

#### 1. Field of the Invention

The present invention relates to an extended release form of Diltiazem, a process for the manufacture thereof and pharmaceutical compositions containing the same.

#### 2. Description of the Background

Diltiazem hydrochloride is used in medicine principally for its calcium channel blocking properties, and, therefore, finds application in the treatment of angina pectoris and hypertension; either alone or in combination with other medications.

Although the mechanism for calcium channel blocking is not completely understood, calcium ion entry is believed to be inhibited through select voltage, with the sensitive areas termed "slow channels", across cell membranes. By reducing intracellular calcium concentration in cardiac and vascular smooth muscle cells, coronary arteries, peripheral arteries and arterioles are dilated and heart rate may be reduced. Also, myocardial contractibility may be decreased and atrioventricular nodal conduction may be slowed. The activity of diltiazem in human is directly related to its blood or plasma concentration.

For illnesses which require continuous and constant control, such as hypertension and angina pectoris, Diltiazem must be administered every 6 to 8 hours, as it has a very short half-life in blood of only about 3 to 4 hours. However, such frequent administration times render the treatment very annoying or even impossible to effect, particularly during the night. Further, after each administration of an immediate-release galenic form of Diltiazem, which generally is necessary four times per day, a succession of rapidly increasing and decreasing plasmatic Diltiazem concentrations are established. Thus, the organism being treated and the target organ, more particularly the heart, are alternatively subjected to overdoses and to underdoses of medicine.

In order to alleviate these drawbacks, a first galenic form of sustained-released of Diltiazem known under the trade name CARDIZEM SR® was developed and presented in the form of "erodible pellets", U.S. Pat. No. 4,721,619. Although this form affords a reduction in peak concentration and in the number of daily intakes from 4 to 2, it does not eliminate high Diltiazem blood concentration between successive medication intakes. Hence, the patient is still obliged to take the medication twice daily. The products as described in U.S. Pat. No. 4,721,619 are prepared by a building up process which requires, as described therein, between 50 and 200 layers so as to obtain a core which, thereafter, requires between 20 and 40 layers of coating so as to obtain the membrane. Moreover, the solvent of the polymer solution used to make the membrane is constituted by organic solvents, such as isopropanol, methanol, acetone, and methylene chloride which are dangerous to use due to their flammability and toxicity. Such solvents are also environmentally hazardous. Particular care must be taken to avoid any traces of solvent in the final product because these solvents are toxic and are unsuitable in the product which is administered orally.

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Thus, a need continues to exist for a multiple unit extended-release diltiazem hydrochloride galenic form which need be administered only once daily, and from which blood Diltiazem concentrations are not effected by the concomitant intake of food, and, further, which can be made by a process not using organic solvents.

### SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide galenic forms of Diltiazem with extended release of the active substance.

It is also an object of this invention to provide galenic forms of Diltiazem having excellent bioavailability while avoiding plasmatic concentration peaks.

The above objects and others which will become more apparent in view of the following disclosure are provided by an extended-release galenic form of a pharmaceutically acceptable salt of Diltiazem, which comprises beads containing the pharmaceutically acceptable salt of Diltiazem as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates the effect of the present invention in gradually releasing Diltiazem in a relatively uniform manner over a period of about one day after the 8th once daily administration in comparison with the effect of a conventional product after the 8th day of administration twice daily.

FIG. 2 illustrates in the solid curve, the mean plasma levels obtained when the product of the present invention is taken without food. The dotted curve represents mean plasma levels obtained when the product is taken with food.

### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Diltiazem or (2S-cis)-3-(Acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2,4-methoxyphenyl)-1,5-benzothiazepin-4(5H) has been known for more than 20 years. The synthesis thereof is described in German patent 1,805,714, corresponding to U.S. Pat. No. 3,562,257.

The present invention relates to novel galenic forms of Diltiazem being characterized by having an extended-release of the active substance. These galenic forms afford excellent bioavailability while avoiding plasmatic concentrations peaks, so that it is now possible to maintain diltiazem plasmatic concentrations in a desired, effective range while simplifying the administration of the medicine to only once daily.

According to the present invention, the Diltiazem extended release galenic forms are substantially characterized by the fact that they are constituted by beads containing a pharmaceutically acceptable salt of Diltiazem as an active substance, associated with at least a wetting agent, the beads being covered with a microporous membrane constituted by at least a water-soluble or water-dispersible polymer or copolymer such as a copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, and a pharmacologically acceptable adjuvant.

In accordance with the present invention, any pharmaceutically acceptable salt of Diltiazem may be prepared in extended release form. For example, such salts may include the hydrochloride, sulfate or phosphate salts. However, they

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may also include the acetate, citrate or lactate salts, for example. It is preferred however, that the hydrochloride salt be used.

In more detail, the microporous membrane whereof the Diltiazem containing microgranules are covered, is constituted by a mixture of a water-soluble and/or water-dispersible copolymer and including at least one adjuvant which may be plastifying agents, pigments, fillers, wetting agent lubricants and antifoam agents.

The active substance containing beads are presented in form of spherules the diameter of which is between about 0.05 mm and 3 mm, preferably between about 0.1 mm and 2 mm.

Among the wetting agents associated with the Diltiazem or salt thereof in the beads, the following compounds may more particularly be exemplified:

- saccharose, mannitol, sorbitol;
- lecithins;
- polyvinylpyrrolidones;
- C<sub>12</sub> to C<sub>20</sub> fatty acid esters of saccharose, commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.);
- xylose esters or xylites;
- polyoxyethylenic glycerides;
- esters of fatty acids and polyoxyethylene (Brijs, Renex and Bumulgines, Henkel, RFA);
- sorbitan fatty acid esters (Span, Atlas, U.S.A.);
- polyglycides-glycerides and polyglycides-alcohols esters (Gelucires, Gattefosse, France).

In addition to at least one of the above named wetting agents the beads may contain excipients or carriers, such as: Microcrystalline celluloses, such as Avicel products (FMC, U.S.A.); methylcelluloses, carboxymethylcelluloses, hydroxyethylcelluloses (Natrosol, Hercules, U.S.A.), hydroxypropyl celluloses (Klucels, Hercules, U.S.A.); and starches.

Among the water-soluble and/or dispersible film forming polymers or copolymers constituting the microporous membrane, may be mentioned particularly polyacrylates and polymethacrylates of the Eudragit type, such as Eudragit E30D, L30D, RS-30 D of Röhm Pharma (RFA), ethylcelluloses, such as Ethocels of DOW, U.S.A. and such as AquaCoat of FMC, U.S.A., Hydroxypropyl cellulose and hydroxypropylmethylcellulose and their derivations.

These polymers or copolymers may be associated into the microporous membrane with at least one adjuvant as exemplified by the following:

- plastifying agents, such as triacetin, dibutylphthalate, dibutylsebacate, citric acid esters, polyethyleneglycols, polypropyleneglycols and polyvinylpyrrolidone;
- pigments, such as iron oxides and titanium oxide;
- fillers, such as lactose and sucrose;
- wetting agents, such as surfactive agents of the Span and Tween types, namely partial esters of fatty acids (lauric, palmitic, stearic and oleic acids) and anhydrides of hexitols derived from sorbitol possibly containing polyoxyethylenic chains, preferably surfactive agents of the Tween type, namely Tween 80, as well as polyethyleneglycols;
- lubricants, such as magnesium stearate and talc;
- antifoaming agents, such as silicone oil.

In addition to the polymer or copolymer, the microporous membrane contains, preferably, talc and/or magnesium stearate as a lubricant, polyvinylpyrrolidone as a plastifying

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agent, titanium dioxide as a pigment, Tween 80 as an emulsifier, and silicone oil as an antifoaming agent.

Generally, the thickness of the microporous membrane is expressed by the percentage of the coating applied to the uncoated beads.

The weight of the microporous membrane may be 2 to 35%, preferably, 5 to 22%, of the weight of said microgranules. These beads may contain the Diltiazem salt in an amount of 20 to 95% by weight, preferably 30 to 85% by weight. The microporous membrane may contain 5 to 95% and, preferably, 30 to 90% of polymers, polymer mixture or copolymers.

The invention relates also to a medicine containing Diltiazem or salt thereof for extended release, the medicine being constituted by beads containing the Diltiazem or salt, such as the hydrochloride, and at least a wetting agent, coated with at least one polymer-based microporous membrane, the coated beads being contained in capsules, little bags or dosage dispensers.

The present invention relates also to a process for obtaining novel forms of a Diltiazem or salt thereof having extended-release in the gastro-intestinal tractus, said process entailing preparing beads and coating the same with a single microporous membrane.

The beads of the Diltiazem or salt thereof may be prepared using a conventional technique. A first technique consists in mixing the Diltiazem or salt thereof with the wetting agent(s) in a melted or finely divided form, or in solution, in the presence of a solvent, such as water, so as to obtain an extrudable paste or plastic mass. Said paste is thereafter extruded in an extruder and then rendered spherical. Several extruder types are usable, for example the extruder of ALEXANDER WERK (RFA) or the apparatus called X-truder of FUJI-PAUDAL (Japan). For obtaining microspheres or beads from the extruded product provided in the form of spaghetti, an apparatus called "spheronizer" (CALEVA Great-Britain) or MARUMERIZER (FUJI-PAUDAL Japan) type is used.

Another conventional technique for obtaining beads consists in spraying and/or dusting cores obtained through agglomeration of the Diltiazem or salt thereof, such as the chlorohydrate, contingently mixed to at least a wetting agent, with a dispersion or solution of at least one wetting agent, for example in a known pilling turbine or in a granulating apparatus, such as the CF granulator system of FREUND INDUSTRIAL CO. (Japan), or in a known planetary granulator such as the collette (Belgium) type.

The obtained beads are dried by any means, for example in an oven or by means of a gas in a fluidized bed.

Finally, said beads are calibrated to the necessary diameter by passage through appropriate screens.

A pasty or plastic mixture, appropriate to be granulated by means of anyone of the above described techniques, may contain the following weight proportions of the Diltiazem or salt thereof, wetting agents and carriers or excipients:

- 20 to 85%; Diltiazem hydrochloride
- 2 to 20% sucroesters WE 15 (wetting agent);
- 5 to 25% Avicel PH 101 (microcrystalline cellulose of FMC, U.S.A.);
- 2 to 10% Methocel E 5 (hydroxypropylmethylcellulose of DOW, U.S.A.);
- 1 to 15% polyvinylpyrrolidone and
- 5 to 40% distilled water.

Said microporous membrane may be applied onto said beads by pulverizing an aqueous solution or dispersion of at least one of the above-named polymers and at least one of the above-mentioned adjuvants onto said beads. This pul-

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verization may be carried out by spray-gunning or by pulverizing the above-named dispersion into a turbine or fluidized bed.

Generally, the present extended release form composition of Diltiazem salt is administered orally. The dosage amount is subject to the response of the individual patient, however, in general, from about 120 mg to about 480 mg per day of Diltiazem salt is administered per day per patient in total.

Additionally, the extended release form composition of the present invention may include other pharmaceutically active ingredients than the Diltiazem salt, provided that the other active ingredient is not pharmaceutically incompatible with the Diltiazem salt.

For example, other pharmaceutically active ingredients, such as  $\beta$ -adrenoceptor blocking agents or diuretics may be used in the present compositions. However, these are only example and are not intended to be limitative.

As examples of  $\beta$ -adrenoceptor blocking agents, drugs such as Propranolol, Atenolol, Labetalol, Prindolol or Sotalol may be used, for example.

As examples of diuretic agents, drugs such as Hydrochlorothiazide, Furosemide, Ethacrynic Acid or Chlorothiazide, for example.

Further, the additional associated drugs may be present in extended-release form also, if desired, however, they need not be.

The present invention will now be further illustrated by reference to certain examples which are provided solely for purposes of illustration and are not intended to be limitative.

According an illustrative embodiment of the present invention, said microporous membrane may be obtained, starting from an aqueous dispersion which contains by weight:

- 10 to 70 Eudragit E30D (polymer)
- 0.5 to 15% talc (lubricant)
- 0.5 to 15% Titanium dioxide (lubricant)
- 0.5 to 15% Magnesium stearate (lubricant)
- 0.5 to 15% polyvinylpyrrolidone (plastifying agent)
- 0.01 to 2% silicone oil (antifoaming agent);
- 0.05 to 5% polysorbate 80 (wetting agent)
- 10 to 70% water (carrier)

### EXAMPLES

The present invention will now be further illustrated by reference to certain examples, which are provided solely for purposes of illustration and are not intended to be limitative. In particular, examples are provided for Diltiazem Hydrochloride extended release galenic forms, a process for preparing the same, therapeutic applications therefor and pharmacokinetic controls using the present galenic forms.

#### Example 1—beads manufacture

Diltiazem hydrochloride	1120 g
Lactose	119 g
Microcrystalline cellulose (Avicel pH 101)	140 g
Povidone k 30	21 g

After introducing the powders into a planetary mixer and granulating same through the obtained plastic mass is extruded through a cylinder with 1 mm diameter holes (Alexanderwork). The small cylinders are rounded, so as to obtain beads, by means of a spheronizer. After drying at 60° C. for 12 hours the beads are sifted and the fraction with size

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comprised between 0.7 mm and 1.4 mm are retained. 1,179 g of beads were obtained yield (84%).

#### Example 2

Diltiazem Hydrochloride	560 g
Crodesta F 160	59.5 g
Microcrystalline cellulose (Avicel pH 101)	70 g
Povidone k 30	10.5 g

The ingredients are introduced in a planetary mixer and dry mixed during approximately 15 minutes. Thereafter 100 ml water USP is added and the mixing is pursued during 10 minutes more until a plastic mass is obtained. This mass is then extruded through a Fuji Paudal extruder equipped with a 1 mm screen so as to obtain "spagetties". A spheronizer type caleva is used so as to transform the extruded product in beads. After drying during 12 hours, on trays, in an oven at 60° C. the beads are sieved so as to eliminate the ones with a size larger than 1.4 mm and with a size smaller than 0.7 mm. The amount of beads obtained with size comprised between 0.7 mm and 1.4 mm was 639.1 g (yield 91.3%).

#### Example 3

Beads prepared in Example 1 were coated in a STREA-1 (Aeromatic) fluidized bed using the "Top spraying" technic. 440 g of coating suspension of the following composition was applied on 500 g of beads. Thereafter the coated beads were dried at 50° C. during 16 hours.

Coating suspension composition:

Magnesium stearate	12.5 g
Titanium dioxide	5.0 g
Povidone k 30	5.0 g
Eudragit NE30D	620.0 g
Talc USP	17.5 g
water	338.0 g
Simethicone	1.0 g
Tween 80	0.8 g

"In vitro" dissolution were obtained using the apparatus #2 as described in the United States Pharmacopeia. The 900 ml dissolution medium consisted of a phosphate buffer pH 5.8 and the revolution speed 100 rpm.

elapsed time [h]	percent dissolved [%]
1	5
4	34
8	62
12	84

#### Example 4

The beads as in Example 2 were coated using a fluidized bed coater equipped with a "wurstler" system. 8 kg of uncoated beads were introduced in an Aeromatic Aerocoater and 2.77 kg of the following coating suspension was applied at a rate of 30–35 g per minute. Thereafter the coated beads were dried during 15 hours at 45° C.

Coating suspension:

Magnesium stearate	0.636 kg
Talc	0.636 kg

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-continued

Titanium dioxide	0.0909 kg
Hydroxypropylmethylcellulose	0.200 kg
Polysorbate 80 NF	0.007 kg
Simethicone c emulsion	0.018 kg
Eudragit NE 30 D	12.4 kg
purified water	6.7 kg

## Dissolution "in vitro"

The results were obtained using the same equipment as in Example 3. The dissolution medium was composed of 900 ml of water and the temperature was maintained of  $37 \pm 0.5^\circ \text{C}$ .

elapsed time [h]	percent dissolved [%]
2	9
4	33
6	54
8	82

## Pharmacokinetical results

The new galenic form of Example 4 was the object of a pharmacokinetical study in comparison with a form in accordance to the prior art as described in U.S. Pat. No. 4,721,619. (Cardizen SR®) therefore 6 healthy subject received successively in a random order 300 mg of each of the 2 products. The product of Example 4 was administered at a dose of 300 mg once daily while the product on the market was administered twice daily at a dose of 150 mg (300 mg daily total dose) during 7 days. At each of the eight day, 11 samples of blood were withdrawn when product of Example 4 was administered and 15 blood samples were withdrawn after the Cardizen SR® administration. Diltiazem plasma levels were assayed using a specific high pressure liquid chromatographic method. FIG. 1 shows the results obtained: the continuous line represent the Diltiazem plasma levels obtained with the product of Example 4 and the broken line the Diltiazem plasma levels of Cardizen SR®.

FIG. 1

Pharmacokinetical parameters:			
	Units	Example 4	Cardizen SR®
Area under the curve [0-24 h]	mg.h/ml	$2782 \pm 1037$	$2864 \pm 1222$
Maximal concentration	mg/ml	$116.3 \pm 54.1$	$192.7 \pm 85.3$
Time of maximum concentration	h	$8.0 \pm 1.8$	$5.2 \pm 2.8$
Fluctuation	%	$85.7 \pm 25.7$	$109.5 \pm 25$
Time during the concentration is above 75% of the maximum concentration	h	$9.8 \pm 2.3$	$6.7 \pm 3.7$

From these results the following conclusion can be drawn:

First, FIG. 1 shows that the Diltiazem plasma levels obtained after a once daily administration of one of the products of the present invention are comparable to the ones obtained after a twice daily administration of the product of the previous art.

Second, the bioavailability, expressed by the areas under the curve of the 2 products, is equivalent (no statistical detectable difference).

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Third, the maximal concentration and the fluctuations obtained after a once daily administration of the product of the present invention is lower than the one obtained with Cardizen SR® after a twice daily administration.

Fourth, the time during the concentration is above 75% of the maximum concentration is 46% longer after the once daily administration of the product of the present invention than with product of the previous art when given twice daily.

## Food effect study

The product of Example 4 was given to 24 healthy volunteers and the bioavailability was measured after single oral dose of 300 mg given with and without food.

The clinical trial was conducted as an open, single dose, randomized, cross over study. Blood samples were obtained before and until 36 hours after the administration. The experiment was repeated in the same subjects with the other treatment at an interval of 7 days. The plasma concentration of Diltiazem was determined in all available samples using an HPLC method. Pharmacokinetics parameters were derived from the individual plasma concentration versus time profiles and statistically compared for treatment differences and assessment of bioequivalence. FIG. 2 curves shows the mean plasma levels obtained when the product is taken without food and the dotted curve the mean plasma levels obtained when the product is taken with food.

FIG. 2

Pharmacokinetics parameter - product of Example 4			
	Units	Fasting	Food
Area under the curve (total)	mg. h/ml	$1988 \pm 119$	$1925 \pm 109$
Mean residence time	h	$21.3 \pm 0.7$	$19.9 \pm 0.9$
$K_a$	$\text{h}^{-1}$	$0.283 \pm 0.024$	$0.300 \pm 0.027$
Maximum concentration	mg/ml	$100 \pm 4.8$	$112 \pm 5.9$

No statistical difference was detectable. The product of Example 4 given with food is bioequivalent to the administration without food to within less than 20% regarding area under the curve, mean residence time and maximum concentration. The larger interval obtained for  $K_a$  was due to the higher variability of this parameter, the difference between the treatment means remaining small (6%).

From all the results it appears clearly that the product of the present invention can be administered once a day and that the plasma concentration variations are lower than the one obtained with the conventional product given twice a day.

Having described the present invention, it will now be apparent to one skilled in the art that many changes and modifications may be made to the above-described embodiments while remaining within the spirit and the scope of the present invention.

What is claimed as new and desired to be secured by Letters Patent of the United States is:

1. An extended-release galenic composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient, each bead containing one or more of the Diltiazem salts and an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract

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or other adverse conditions which the composition will meet therein, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water-, acid- and base-insoluble polymer and a pharmaceutically-acceptable adjuvant,

and wherein the wetting agent is selected from the group consisting of sugars, C<sub>12</sub>-C<sub>20</sub> fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins and a combination thereof.

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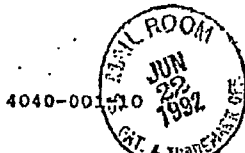
2. The composition of claim 1, wherein the wetting agent is a sugar.

3. The composition of claim 1, wherein the effective amount of the wetting agent is about 8% by weight of the composition.

4. The composition of claim 1, wherein the wetting agent is sucrose stearate, the water-soluble or water-dispersible polymer or copolymer is hydroxypropylmethyl-cellulose and the water, acid- and base-insoluble polymer is an acrylic polymer.

\* \* \* \* \*

# EXHIBIT 2



IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :

ARTHUR M. DEBOECK ET AL :

SERIAL NO: 07/721,396 :

FILED: JUNE 26, 1991 :

FOR: EXTENDED RELEASE FORM  
OF DILTIAZEM

: GROUP ART UNIT: 1502

: EXAMINER: SPEAR

RECEIVED  
JUN 29 1992

GROUP 150

AMENDMENT

HONORABLE COMMISSIONER OF PATENTS & TRADEMARKS  
WASHINGTON, D.C. 20231

SIR:

Responsive to the Official Action of March 23, 1992, on  
the above-identified application, reconsideration is  
respectfully requested.

IN THE SPECIFICATION

Page 6, line 9, prior to "saccharose," insert --sugars,  
for example--, same line, after "sorbitol", delete ";" and  
insert --and lactose;-- and  
line 11, delete "polyvinylpyrrolidones".

IN THE CLAIMS

Please cancel Claims 1-11 without prejudice and insert  
therefor the following new claims:

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12  
a) --12. An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem, which comprises beads, said beads comprising:

a) an effective amount of said one or more Diltiazem salts as an active ingredient, and  
 b) a wetting agent, wherein said wetting agent comprises a sugar, a  $C_{12}$ - $C_{20}$  fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester, or lecithins, <sup>and</sup> or any combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant.

13. The extended-release galenical composition of Claim 12, wherein said salt is the hydrochloride salt.

14. The extended-release galenical composition of Claim 12, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

15. The extended-release galenical composition of Claim 14, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

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16. The extended-release galenical composition of Claim 12, wherein the weight of the Diltiazem salt is about 20 to 95% by weight.

17. A pharmaceutical composition comprising an extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem, which comprises in capsule form:

a) beads comprising an effective amount of one or more pharmaceutically-acceptable salts of Diltiazem and a wetting agent, wherein said wetting agent comprises a sugar, a  $C_{12}$ - $C_{20}$  fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester, or lecithins, or any combination thereof;

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant, and

b) one or more other pharmaceutically active ingredients which are pharmaceutically compatible with said one or more Diltiazem salts.

18. The pharmaceutical composition of Claim 17, wherein said one or more other pharmaceutically active ingredients

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comprise  $\beta$ -adrenoceptor or diuretic compounds or compositions containing the same.

19. The pharmaceutical composition of Claim 17, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

20. The pharmaceutical composition of Claim 17, wherein said salt is the hydrochloride salt.

21. The pharmaceutical composition of Claim 17, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

22. A method for treating angina pectoris or hypertension or both in a mammal, which comprises administering to said mammal an effective amount of an extended-release galenical composition of Diltiazem or a pharmaceutically-acceptable salt thereof and a wetting-agent in the form of beads, wherein the wetting agent comprises a sugar, a  $C_6$ - $C_{20}$  fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester, or lecithins, or any combination thereof,

wherein the beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant.

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23. The method of Claim 22, wherein said administration is orally and once per day.

24. The method of Claim 22, wherein said mammal is a human.

25. The method of Claim 23, wherein from about 120 mg to about 480 mg of said one or more Diltiazem salts are administered in total per day.

26. The method of Claim 22, wherein said salt is the hydrochloride salt.

27. An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem, which comprises beads containing:

- a) an effective amount of said one or more Diltiazem salts as an active ingredient, and
- b) a wetting agent, wherein the wetting agent comprises a sugar, a  $C_{12}$ - $C_{20}$  fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, alcohol-polyglycide ester or lecithins, or any combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant, wherein the membrane is adapted to release Diltiazem, in 900 ml of water when USP

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XXII, apparatus no. 2 is used at 100 rpm, at a rate in the order of:

9% after 2 hours,  
33% after 4 hours,  
54% after 6 hours, and  
between 62% and 82% after 8 hours.

28. The extended-release galenical composition of Claim 27, wherein said salt is the hydrochloride salt.

29. The extended-release galenical composition of Claim 27, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

30. The extended-release galenical composition of Claim 29, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.--

#### REMARKS

Claims 1-11 have been cancelled. New Claims 12-30 have been added. Hence, Claims 12-30 are now active in this application.

#### REQUEST FOR RECONSIDERATION

Diltiazem hydrochloride is used as a medicine primarily for its calcium channel blocking properties. It, therefore, finds application in the treatment of angina pectoris and hypertension.

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Both hypertension and angina pectoris require continuous and constant control, however. Thus, Diltiazem must be administered every 6-8 hours, as it has a very short half-life in blood of only about 3-4 hours. Unfortunately, such frequent administration times render Diltiazem administration very annoying or even impossible to effect, particularly during the night.

Although these drawbacks have been eliminated to some extent using a known galenic form of sustained-release Diltiazem, using this form still requires that the patient take the medication twice daily. Further, the process by which this product is prepared requires the use of organic solvents which are dangerous to use due to their flammability and toxicity, and which pose environmental hazards in their disposal.

In accordance with the present invention, however, a multiple unit extended-release Diltiazem galenical form is provided which need be administered only once daily. Moreover, the process by which this product is made does not use organic solvents.

In particular, and in part, the present invention provides an extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem, containing beads, the beads containing:

- a) an effective amount of one or more Diltiazem salts as an active ingredient, and

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b) a wetting agent, wherein the wetting agent comprises a sugar, a  $C_{12}$ - $C_{20}$  fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins, or any combination thereof, wherein the beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant.

Thus, at the outset, it is noted that the present composition is characterized by the use of i) a wetting agent, and ii) a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate.

Furthermore, by the very nature of the process by which the present beads are made, the beads produced are homogeneous. Their homogeneity arises from the extrusion-spheronization process by which they are made.

Claims 1-5 and 8-11 stand rejected under 35 U.S.C. 102(e) as being anticipated by Debregeas et al. However, this reference neither discloses nor suggests the present invention.

Particularly, Debregeas does not disclose a wetting agent. Debregeas discloses the use of polyvinylpyrrolidone as a binder, as does Applicant-as a binder and as a plastifying

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agent (see page 8, line 4 and compositions at pages 10 and 12 of the application) not as a wetting agent. The reference to polyvinylpyrrolidone at page 6, line 11 has been deleted. This deletion is consistent with the teachings in the application at page 8, line 4 (at pages 10 and 12).

Debregeas et al discloses a slow-release preparation of Diltiazem which agglomerates Diltiazem on a neutral core, such as sugar, with the assistance of polyvinylpyrrolidone. This process commencing with a neutral core is generally known as the "building-up" process. The pellets so obtained are coated with an organic solution of shellac and ethyl cellulose, or a dispersion of ethyl cellulose. Also, acrylic acid esters and methacrylic acid esters having a low content of quaternary ammonium groups may also be used with organic solvents such as lower alcohols, acetone and ethyl chloride. Hence, this process is representative of the conventional process which uses organic solvents. This is avoided by virtue of the present invention.

Furthermore, the "in vitro" release of products according to Debregeas et al is extremely dependent on the medium and conditions used for testing. Also, the "in vivo" performance of such a product is ascertainable only after a correlation of in vivo/in vitro has been established, if this is even possible! Debregeas et al discloses the use of the USP XXI method, as such a method of correlation.

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However, after careful review of the USP XXI method, the present inventors have not been able to find any method of dissolution for Diltiazem. In fact, Diltiazem is not even listed in USP XXI. Further, Annex II shows that Diltiazem was incorporated into USP XXII, which only became official on January 1, 1990, two years after Debregeas et al filed their application. Further, it was not until Supplement 6 became official in March of 1992 that the artisan could have found any method of dissolution for Diltiazem extended-release. Thus, Applicant must ask by what method was the dissolution data of Claim 1 of Debregeas et al generated?

Further, the galenical Diltiazem preparation described by Debregeas et al clearly does not disclose a Diltiazem bead composition containing a wetting agent, prepared by the extrusion spheronization process. Such a bead composition is necessarily a homogeneous bead composition. By contrast, the "building-up" process described by Debregeas et al is of no utility for the present invention as the present invention does not use the "building-up" process.

Furthermore, at column 7, line 65, Debregeas et al describes that:

... the microgranules can be prepared by extrusion followed by rounding.

No further description is given. In fact, such a procedure is impossible as microgranules of the type constituted by a central core as in Debregeas et al cannot be produced by the extrusion-spheronization process. By

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contrast, in accordance with the present invention, the extrusion-spheronization process leads to homogeneous type beads while the "building-up" process, starting with a sugar core, leads to heterogeneous type beads. Clearly, it is impossible to have a sugar central core in a homogeneous bead as in the present invention. Such a bead is, by nature, heterogeneous.

Further, the advantages of the present extrusion-spheronization process versus the building-up process of Debregeas et al may be noted as follows. Namely, for the present process:

a) there is no need of a central core,  
b) the present process is less time consuming: The building-up process of Debregeas et al requires between 50 and 200 layers to be applied successively and the preparation of each layer requires:

1. Wetting the beads with a polymeric solution, wherein the solvent wets the beads and the polymer acts as a "glue",
2. Powdering with the substance, and
3. Drying the beads so as to evaporate completely all the solvents.

c) The extrusion-spheronization process permits the use of water as solvent, without any drawbacks while in the building-up process the use of water increases dramatically the process time.

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Further, the use of water as solvent in the present process has the following Advantages:

1. water is very inexpensive,
2. water is non-toxic and does not require complete removal from the pharmaceutical formulation and does not require special protection equipment for the operators during the process,
3. water is non flammable. This drastically reduces the fire protection equipment needed during the process, and
4. water is the only environment friendly solvent.

Because of the limitations on solvent emission in most countries worldwide, this process can be used practically everywhere.

d) Further, the extrusion-spheronization permits working in very large batches; the batch size is only dependent on the mixer size.

e) Finally, the extrusion-spheronization process can be adapted to the continuous production of beads.

Additionally, Debregeas et al neither describes nor suggests the use of an aqueous dispersion a neutral copolymer of ethylacrylate and methyl methacrylate (Eudragit NE30D) as in the present invention. The Eudragits described by Debregeas are copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups (Eudragit RS and RL) which can only be used in solutions with organic solvents. The environmental and toxicity concerns

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expressed in the present application are neither noted nor addressed by Debregeas et al.

Further, at column 3, lines 4 and 10, Debregeas et al describes the composition of the neutral core of saccharose and fructose to start the building-up process with the binder being polyvinylpyrrolidone to make the different layers of product. By contrast, the present invention does not use the building-up process and thus does not make use of a neutral core of saccharose and fructose. Further, Debregeas does not disclose saccharose as a wetting agent. The saccharose contained in the central core of the bead cannot act as a wetting agent because in order to do so the saccharose must be mixed with the Diltiazem and, therefore, saccharose must be in solution with Diltiazem. Unfortunately, in this system saccharose can only end up in solution after all the layers of Diltiazem are dissolved. In other words, saccharose can only become effective when there is not longer a need therefor.

The wetting agents claimed in the present invention are substances which are believed to modify the solubility of Diltiazem inside the coated beads when they are placed in a dissolution medium or when they are ingested by a mammal. This concept is neither disclosed nor suggested by Debregeas et al. Debregeas does not disclose a wetting agent- polyvinylpyrrolidone is not a wetting agent, it is a binder and plastifying agent. More specifically, Debregeas neither discloses nor suggest the use of any wetting agent, let alone

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those comprising a sugar, a  $C_{12}$  to  $C_{20}$  fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols an polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycides, an alcohol-polyglycide esters or lecithins, or any combination thereof.

In fact, since Debregeas et al fails either to disclose or suggest the use of any wetting agent, the teachings thereof would be of no use to the artisan in attempting to arrive at the present invention, which requires the use of wetting agents.

Moreover, the product produced by Debregeas et al may be distinguished from the present product.

One in vivo parameter that permits one to estimate the performance of a sustained release product is the time of maximal concentration,  $T_{max}$ . The most significant values of  $T_{max}$  are obtained after multiple administrations.  $T_{max}$  measured after multiple administrations of the product of the present invention (see page 17) is  $8.0 \pm 1.8$  h. The  $T_{max}$  observed with Cardizen SR, a conventional product administered twice daily was  $5.2 \pm 2.8$  h. These data show clearly that the product of the present invention is much more adapted for administration once daily than that obtained by Debregeas et al. Moreover Debregeas et al obtain values of  $T_{max}$  which are somewhat lower,

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but comparable to the ones obtained with Cardizen SR, which is a product designed and approved by the U.S. FDA for use.

As a further comparison, the following values are noted:

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Debregeas patent: $T_{max}$ after multiple administrations			
[h]			
	TABLE II	TABLE IV	
Coating	Shellac Ethylcellulose	Shellac	Aquacoat Aquacoat (ethylcellulose dispersion)
180 mg	4.7		5.5
240 mg	4.95		
300 mg	6.6	4.2	3 - 5.6
Mean $T_{max}$ = 4.93 $\pm$ 1.45 h.			

Thus, the present compositions are not only clearly different from but surprisingly superior to those of Debregeas et al.

Notably, the  $T_{max}$  values recited above are comparable to those reported for Cardizen SR. This is not surprising, however, as Debregeas et al is representative of a conventional "building-up" process.

Hence, this ground of rejection is believed to be unsustainable and should be withdrawn.

Claims 5-7 stand rejected under 35 USC 103 as being unpatentable over Debregeas et al in view of Joshi et al. However, the latter reference fails to overcome the deficiencies of the former.

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In particular, Joshi describes modified-release formulations in the form of extruded spheronized beadlets from which medicament is released at a controlled rate, the beadlets containing:

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- a) from 3 to 60% of medicament,
  - b) <sup>from</sup> ~~form~~ 5 to 50% of an organic carboxylic acid, and
  - c) non-lipophilic non fat binder, wherein
  - d) said beadlets having a hardness of at least 2 strong cobbs units.

Joshi does not, however, describe or suggest an extended release formulation, but this is not the purpose of Joshi. The only word used in the disclosure is "modified release". However, no description is provided of any sustained release properties, such as in vitro or in vivo data. It is submitted that this is because no such properties exist for these compositions. For example, if example 9 is considered, which relates to a Diltiazem formulation the composition is:

CONSTITUENT	PARTS BY WEIGHT
Diltiazem	20
Citric acid	30
Microcytalline cellulose	43
TOTAL	93

This formulation will be relatively hygroscopic due to the high citric acid content and the Diltiazem from these beads will be released extremely fast. In water for example, not more than 30 minutes would be required to release at least 80%

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of the Diltiazem. However, this is exactly what the artisan would do in order to obtain an extremely fast Diltiazem release formulation!

It is known by the artisan, that every sustained release drug is a new system by itself. This is due to the very large number of parameters which must be taken in consideration such as: physico-chemical properties (solubility, crystallinity, pH, pKa...) pharmacokinetical properties (absorption, distribution, metabolization, first pass effect, elimination, recirculation, efficacy and toxicity limits..) and medical properties (effect of drug, effect of metabolites, side-effects, shape of clinically desired blood concentrations profiles...). Joshi cites a list of drugs from column 8, line 40 to column 9, line 20; i.e., about 130 different products. This is simply a product listing wherein products appear such as: "basic salts like alkali metal salts". However, this would be of no help to the artisan as when mixed with organic carboxylic acids in water, such salts would undergo a neutralization reaction.

In fact, the present invention does not use organic carboxylic acids therein, whereas in the Joshi process this is essential. See column 9, line 52-54 and Claim 1. Moreover, Joshi does not disclose the use of a "wetting agent" in the uncoated beads manufacturing process. Further, Joshi does not disclose the characteristics of the obtained products and,

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therefore, one skilled in the art would be unable to know or to understand the advantages and the limits of this patent.

Hence, this ground of rejection is also believed to be unsustainable and should be withdrawn.

In summary, inasmuch as both cited references prepare product by a method different from the present invention, and inasmuch as these processes are incompatible with the present process and further inasmuch as the present product is distinguishable in at least one property over that of Debregeas et al, it is believed that each claimed aspect of the present invention is fully patentable over the cited references.

Additionally, it is noted that support may be found for the term "lactose" in the examples. Furthermore, it is believed that the recitation of the four sugars at page 6 of the Specification is sufficient exemplification to warrant inclusion of the generic term "sugars".


Accordingly, in view of all of the above amendments and attendant remarks, it is believed that the present application

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now stands in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, MCCLELLAND,  
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# EXHIBIT 3

4040-001-10

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :  
ARTHUR M. DEBOECK ET AL : EXAMINER: SPEAR,  
SERIAL NO. 07/721,396 :  
FILED: JUNE 26, 1991 : GROUP ART UNIT: 1502  
FOR: EXTENDED RELEASE FORMS :  
OF DILTIAZEM

DECLARATION UNDER 37 C.F.R. 1.132

HONORABLE COMMISSIONER OF PATENTS & TRADEMARKS  
WASHINGTON, D.C. 20231

SIR:

Now comes Arthur Deboeck who deposes and states:

1. That I am a graduate of Institut HEURICA chimie Brunel (A) and received a Chemical Engineer degree in the year 1970.
2. That I have been employed by and associated with Galephar P.R., Inc for 22 years as a Pharmaceutical Chemist in the field of Pharmaceutical research, development and production, and am one of the present inventors.
3. That the following experiments were carried out by me or under my direct supervision and control:
  - A. In order to demonstrate that the "center" or "core" of the present pharmaceutical composition is an inherently homogeneous or uniform composition of Diltiazem of one or more salts thereof and wetting agent, the following experiment was conducted,

---

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EXPERIMENT 1: HOMOGENEITY OF THE CORE

The product of example 2 of the present specification (the core is also called "uncoated beads") was prepared six (6) times on a larger scale. Thus, in accordance with the present application: 37.6 kg of Diltiazem HCl, 4.7 kg of Microcrystalline Cellulose, 0.705 kg of Povidone K 30 and 4 kg of Sucrose Stearate (Wetting Agent) were mixed in a planetary blender for 15 minutes until the dry blend was homogeneous. 7.3 kg of water was then added and blended for another 20 minutes. The product was thereafter extruded, spheronized and dried.

To assure that the core is perfectly homogeneous, samples from the dry blending (first 15 min.) were removed after 10 and 15 minutes from the front and the back of the top and bottom of the blender. These samples were then tested for homogeneity by measuring the Diltiazem content. If the content of Diltiazem in the mixture is homogeneous, it is clear that the mixture, itself, is homogeneous and that the wetting Agent and all other excipients are homogeneously distributed in the core.

The results obtained are summarized in the following table.

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VERIFICATION OF THE HOMOGENEITY OF THE CORE COMPOSITION FOR 8 BATCHES												
Batch	1		2		3		4		5		6	
Dry Mixing Time												
Dilution content % (calculated on the dried basis)												
mixing time (min.)	10	15	10	15	10	15	10	15	10	15	10	15
top front	81.5	81.0	80.4	81.0	80.8	81.5	79.1	79.3	79.5	79.7	79.2	79.2
top back	81.2	81.0	80.0	81.1	81.0	81.4	79.1	79.0	79.5	79.7	79.1	79.9
bottom front	80.8	81.3	81.0	80.8	80.8	80.9	79.0	79.7	79.4	79.7	79.5	79.4
bottom back	80.3	79.8	81.2	81.0	79.0	81.1	79.9	80.2	79.4	79.7	79.0	79.5
mean	80.9	80.8	80.7	81.00	80.4	81.20	79.5	79.3	79.9	79.7	79.2	79.5
Stdev	0.55	0.62	0.55	0.80	0.91	0.80	0.45	0.65	0.44	0.65	0.26	0.35
%RSD	0.68	0.76	0.68	1.0	1.14	0.94	0.53	0.82	0.56	0.82	0.34	0.32
overall mean	79.7											
overall Stdev	1.17											
overall %RSD	1.47											
End of Wet Granulation												
Dilution content % (calculated on the dried basis)												
top #9	80.0		80.5		80.7		80.5		80.3		79.7	
top #10	80.2		80.7		80.4		80.5		80.0		80.2	
top #11	80.2		80.8		81.7		80.3		80.4		79.7	
bottom #12	80.0		81.1		81.5		79.9		80.5		79.9	
bottom #13	80.1		80.7		81.5		80.3		80.5		80.0	
bottom #14	80.3		80.0		80.9		79.9		80.3		80.0	
mean	80.1		80.8		81.1		80.2		80.3		79.9	
Stdev	0.12		0.39		0.55		0.30		0.19		0.20	
%RSD	0.15		0.44		0.68		0.37		0.23		0.25	
overall mean	80.4											
overall Stdev	0.43											
overall %RSD	0.53											

A relative standard deviation of 0.53%, after the wet granulation mass is produced, assures that the composition of the core is perfectly homogeneous.

It is noteworthy that the uniformity of the blending after granulation is better than after dry blending. This increases the assurance that the components of the core will not separate during the extrusion spheronization process.

This step was carefully evaluated, as can be seen by the amount of analyses performed, as it is essential to the

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performance of the final product that the components of the core be homogeneously mixed.

In order to demonstrate the influence on the dissolution medium of the dissolution profile, the following experiment was conducted.

EXPERIMENT 2:

INFLUENCE OF THE DISSOLUTION MEDIUM ON THE DISSOLUTION PROFILE

The dissolution profile of Diltiazem extended-release coated beads was performed using USP dissolution apparatus 1 with a rotating speed of 100 rpm temperature at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ .

The percent of Diltiazem HCl dissolved was determined by ultraviolet spectroscopy from samples withdrawn after 2, 4, 6, 10 and 22 hours.

Three different aqueous dissolution media were used to measure the profile of a same Lot of coated beads.

Dissolution media used:

1. Water : Purified water > 10 MQ
2. SIF : Simulated Intestinal Fluid  
without enzyme  
= 7.5 pH 0.05M Phosphate Buffer
3. 0.5M Phosphate : 7.5 pH 0.5M Phosphate Buffer  
Buffer

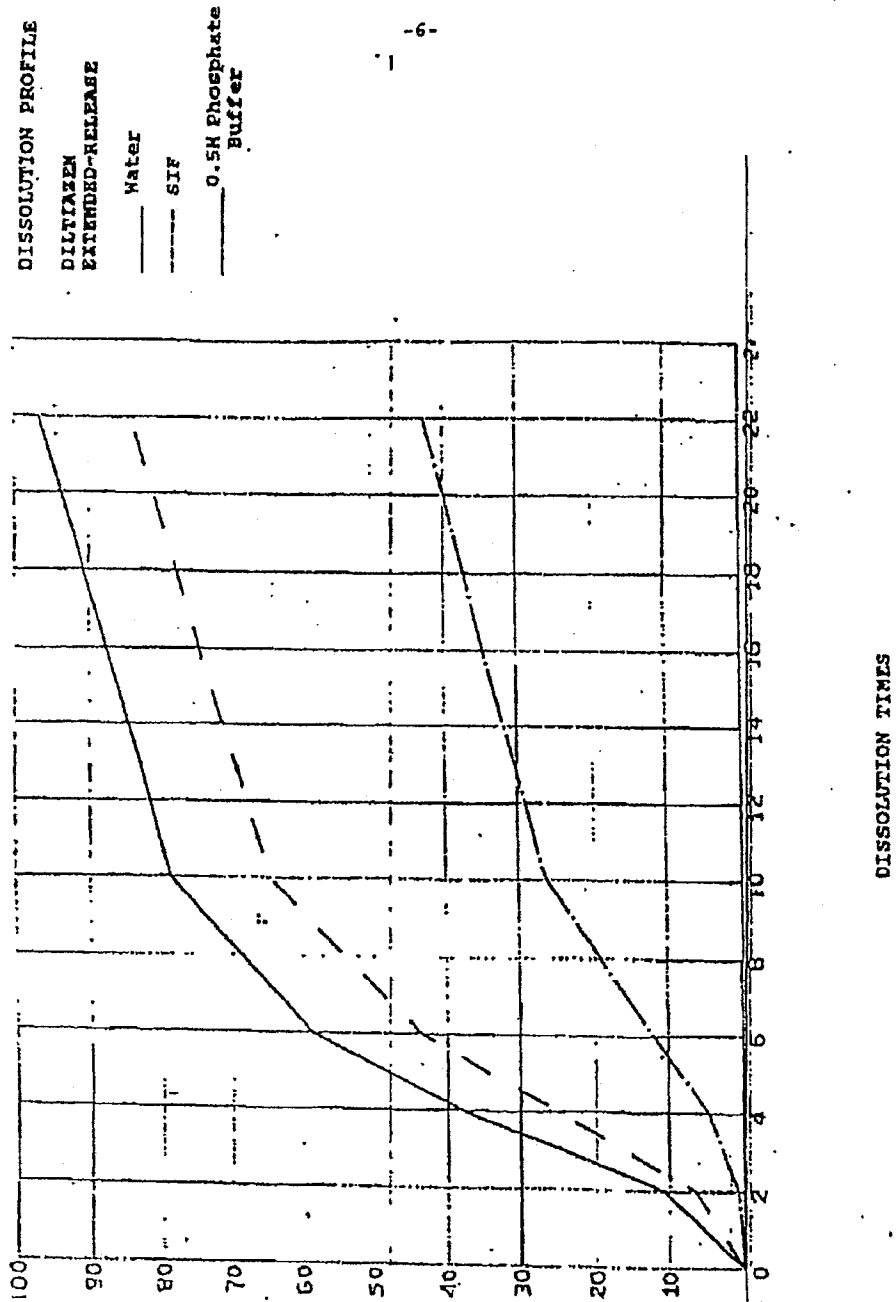
-5-

DISSOLUTION PROFILE OF DILTIAZEM OD ER IN DIFFERENT MEDIA			
Sampling Times (hours)	Percent Dissolved (%)		
	Water	Simulated Intestinal Fluid	7.5 pH 0.5M Phosphate Buffer
3	11	7	1
4	38	25	5
6	59	43	12
10	79	65	26
22	97	84	42

These results show clearly that the dissolution profile of an extended release product is extremely dependent on the medium in which the test is performed. Debregeas et al cites only "an aqueous medium". Notably, the three (3) media used in this small study are all aqueous media and the profiles obtained are very different from each other.

It is common practice for extended release products to use a dissolution test that is discriminant and practical. Therefore, the medium is changed in such a way that the test will be completed in approximately 24 hours. Thus, a report of percent dissolved as a function of time without defining the medium is meaningless.

The dissolution profiles obtained with water, SIF and 0.5 M phosphate buffer are shown in the following figure.



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In order to demonstrate the surprisingly superior bioavailability of Diltiazem from the present pharmaceutical compositions as compared to two other marketed products, the following experiment was conducted.

EXPERIMENT 3:

IN VIVO COMPARISON OF THE PRODUCT OF EXAMPLE 4 WITH TWO APPROVED "ONCE DAILY" PRODUCTS AVAILABLE ON THE U.S. MARKET (CARDIZEM CD AND DILACOR XL)

Fourteen (14) healthy male volunteers were subjected to a steady state bioavailability study comparing the product of Example 4 with Cardizem CD and Dilacor XL. Therefore, during seven (7) days, each volunteer received each of the products at a dose of 240 mg daily.

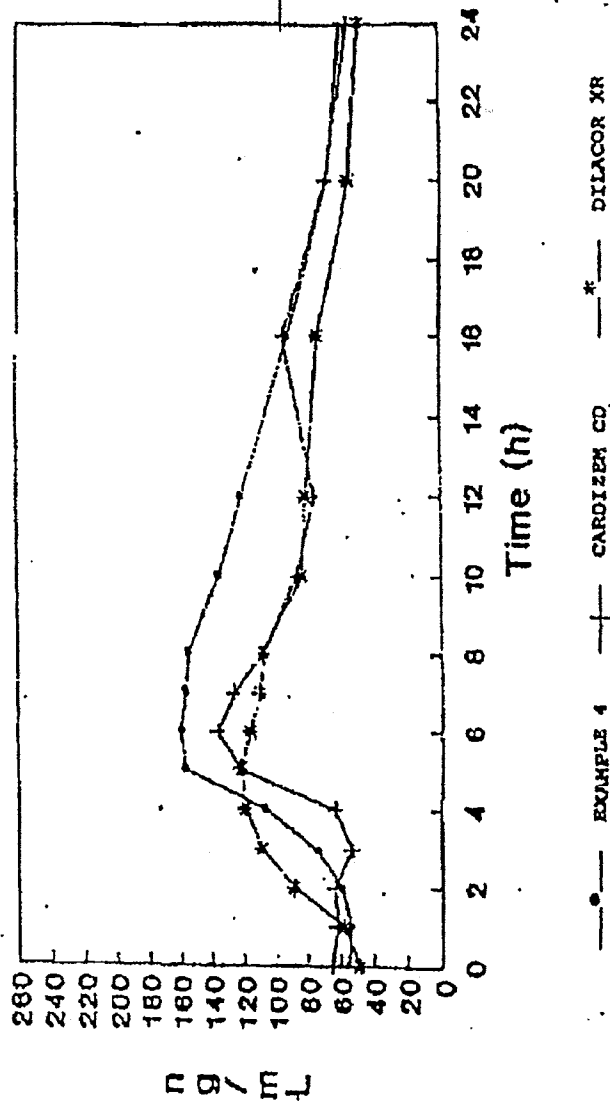
Blood samples on each of the seventh day were removed after 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20 and 24h of administration and Diltiazem concentration was measured. The mean curves for the three (3) products are shown in figure hereafter included.

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PHARMACOKINETICS PARAMETERS OBTAINED			
Parameter	Example 4	Cardizem CD	Dilacor XL
AUC [ng.h/mL]	2400	1964	1901
C <sub>max</sub> [ng/mL]	183	152	131
C <sub>min</sub> [ng/mL]	46	46	44
T <sub>max</sub> [h]	7.0	5.4	5.3

# MEAN PLASMA DILTIAZEM LEVELS

DAY 7, n = 14 subjects



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CONCLUSIONS

1. The product of Example 4 is suitable for "once daily" Diltiazem administration since:

- a)  $C_{min}$  (the minimum concentration 24 hours after administration) value is equal  $C_{min}$  of Cardizem CD and higher than  $C_{min}$  for Dilacor XL; and
- b)  $T_{max}$  (time to reach the maximum concentration) for example 4 is 1.6 hours longer than  $T_{max}$  for Cardizem CD and 1.7 hours longer than  $T_{max}$  for Dilacor XL (this represents a 130% improvement). The longer  $T_{max}$  is, the more sustained is the release of product.

2. The product of Example 4 clearly affords an increased bioavailability versus the two (2) other marketed products. The increase versus Cardizem CD being 122% and versus Dilacor XL 126%. This is indicative of an increased effectiveness for the product of Example 4 versus the 2 current marketed in the U.S. products.

These surprising and significant improvements in pharmacokinetical parameters appear to be due to the characteristics of the products of the present invention, i.e., a homogeneous core containing a wetting agent and the outer coating characteristics.

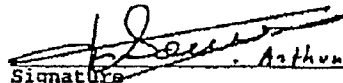
4. On the basis of all of the above, I am of the opinion that the results afforded by the present invention would not

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be expected by the artisan and would, in fact, be quite surprising.

5. The undersigned petitioner declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

6. Further deponent saith not.

  
Signature Arthur Dubuffet  
Date April 20, 93

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"A"  
DEPARTMENT HEALTH & HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

CONFIDENTIAL

Public Health Service

Memorandum

DATE : OCT 15 1991

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approvability of NDA 20-062

TO : NDA 20-062, Diltiazem Sustained-Release Once-a-Day Formulation,  
Cardizem CD file

This memorandum is intended to provide some thoughts that may not be obvious from the existing documentation, being a sentence here or there in the several hundred pages of review materials.

BACKGROUND

That diltiazem is antihypertensive was never in question. The immediate release formulation clearly lowers blood pressure (but in a b.i.d. regimen has insufficient duration of action, so it is not currently approved) and one controlled-release formulation is already approved in a b.i.d. regimen.

The data in this application (NDA 20-062) need to address questions related to dose response and duration of effect when diltiazem is administered in this formulation. There were four, randomized, placebo-controlled, double-blind trials in patients with hypertension that provided data and reasonably answered the relevant questions.

Doses of this once-a-day formulation studied varied from 90 mg to 540 mg of diltiazem once daily. Blood pressure measurements were made at the end of the dosing interval. All doses of diltiazem lowered systolic and diastolic blood pressure more than did placebo (the reduction produced by the 90 mg dose reduction was not statistically significant, but all other comparisons have p values ranging from 0.030 to < 0.001). The effect (i.e., blood pressure lowering) increased with increasing dose and at trough showed no indication of plateauing. At peak effect (measured at 10 hours after dosing), the effects were greater than at trough for every dose and were consistent with (but did not prove) the maximum peak effect occurring at a dose of about 360 mg, administered once a day.

NDA 20-062

Page 2

Ambulatory blood pressure measurements (24 subjects receiving placebo and 24 subjects receiving diltiazem in a parallel trial, about half of the population in each group; diltiazem dose being 360 mg once a day) showed peak antihypertensive effects occurring between 5 and 8 hours (so the above casual blood pressure measurements were two to five hours after peak effect). The time course of effect, for the 360 mg, was in keeping with a once-a-day regimen. However, overall, the ambulatory blood pressure measurements suggested a duration of action that was shorter than 24 hours. This was not in keeping with the end of dosing interval casual blood pressure measurements where the drug effect of 360 mg doses were 7.5 mm Hg (Study DZPR0068) and 4 mm Hg (Study DZPR0067).

There were no obvious dose-related side effects that were observed. Thus, there is nothing in the database that suggests that the largest dose of diltiazem that could be clinically useful was studied. That is, without side effects being dose limiting and with effects continuing to rise as dose was increased, it is reasonable to expect that larger doses (with increasing effect) could easily have been employed.

All of these data are reasonably summarized in the Summary Basis of Approval.

#### SPECIAL ISSUES

##### Two Sustained-Release Formulations

Cardizem SR is a sustained-release formulation currently approved for the treatment of hypertension. Cardizem CD will be the second sustained-release formulation that is intended for the same indication. This can easily be perceived to lead to confusion.

An educational program (mail, advertisements, and detailing) to all health professionals is planned by Marion Merrell Dow to ensure that all health care professionals are aware that there are two sustained-release formulations available and that their dosing intervals are different.

Once Cardizem CD is approved, promotion of Cardizem SR for hypertension will cease and promotion will urge switching from SR to CD for hypertension.

The SR formulation may receive an anti-anginal claim. Marion Merrell Dow thinks it will. When, and if, that occurs, the SR will be promoted for angina only. Thus, although not the best of all possible worlds, the plans of the sponsor are adequate and the existence of two sustained-release formulations does not prohibit approval of Cardizem CD.

NDA 20-062

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Dissolution Specifications

The sustained-release characteristics of the CD formulation depend upon the ratio of two different bulk beads. The two beads differ (in a mean aggregate sense) with respect to the coating of the beads. During manufacture, the coating process, although controlled and appropriate, cannot be expected to produce 100% identical beads. Consequently, the sponsor plans (after the two bead forms are produced) to provide the finished dosage form by varying the proportion of bead 1 and bead 2 by trial and error, using dissolution as the determinant of relative proportion of each bead.

The overall proposal has been found to be acceptable because the sponsor has adequately shown that the dissolution profile of the final product does predict *in vivo* performance. In this work, they have shown that the dissolution of the final product from the 6th hour through 24 hours (900 ml of 0.1 M HCl at 30°C with a paddle speed of 100 rpm) is a good predictor of steady-state  $C_{max}$  and a reasonable predictor of steady-state  $C_{min}$ ; area under the curve is less reasonably predicted.

Our Biopharmaceutics reviewers point out that the dissolution specifications requested by the firm are based upon having a finished product that is within 15% for AUC and 20% for other parameters. Our reviewers thought the specifications should be mainly determined by  $C_{max}$  prediction and that  $C_{max}$  should be within 10% (leading to no greater than a 20% variation from batch to batch of finished product). From the regression equations that were derived by the sponsor from their studies, our Biopharmaceutics reviewers have recalculated the dissolution specifications with the objective of mainly controlling  $C_{max}$  within  $\pm 10\%$ . This seems entirely reasonable.

After discussion of the dissolution specifications with Marion Merrell Dow, it became clear that the specifications suggested by our Biopharm reviewers were, although not unreasonable, impractical. The sponsor's standard procedure is not to release a new lot unless the lot's dissolution falls in a narrower specification for dissolution than the actual regulatory specification. The rules they will follow are clearly specified in the approvable letter. The release specifications are close to (almost identical to) those we specified.

First-Line Therapy

Current labeling for immediate-release diltiazem calls for diltiazem, as an anti-anginal therapy, to be restricted to patients who cannot tolerate therapy or are not getting suitable effect from beta blockers and/or nitrates. Moreover, current labeling

NDA 20-062

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implies that drug interactions are not adequately explored and that safety concerns caused the "second line" labeling.

The current immediate-release labeling is grossly out of date and (by the mechanism of a supplement submitted by the sponsor) is in the process of revision. Diltiazem, as an immediate release or sustained-release formulation, can be suitably used for first-line therapy.

FINAL Action Unresolved

At the time of issuing the approvable letter, CGMP inspection of the manufacturing facility revealed deficiencies. These need correction prior to approval.

RJ 10/15/91

Raymond J. Lipicky, M.D.

cc: Orig. NDA  
HFD-110  
HFD-110/CSO  
HFD-110/RLipicky  
cf: 9/30/91; 10/7/91; 10/15/91

# EXHIBIT 4

1040-001-10

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :  
ARTHUR M. DEBOECK ET AL : GROUP ART UNIT: 1502  
SERIAL NO: 07/721,396 :  
FILED: JUNE 26, 1991 : EXAMINER: SPEAR  
FOR: EXTENDED RELEASE FORM  
OF DILTIAZEM

RECEIVED  
APR 28 1993  
GROUP 1502

AMENDMENT AFTER FINAL REJECTION

HONORABLE COMMISSIONER OF PATENTS & TRADEMARKS  
WASHINGTON, D.C. 20231

SIR:

Responsive to the Official Action of September 25, 1992,  
on the above-identified application, reconsideration is  
respectfully requested.

IN THE CLAIMS

Please cancel Claims 12, 30 without prejudice and insert  
therefor the following new claims:

cm : 12/30. An extended-release galenical composition of  
Diltiazem or one or more pharmaceutically-acceptable salts  
thereof, which comprises beads, said beads consisting  
essentially of in admixture together:  
p(a) an effective amount of Diltiazem or said one or more  
salts thereof as an active ingredient, and

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19 p1 b) an effective amount of a wetting agent, wherein said wetting agent is selected from the group consisting of a sugar, a  $C_{12}$ - $C_{20}$  fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride, polyglycide, an alcohol-polyglycide ester, lecithins and a combination thereof,

p1 wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl acrylate, and a pharmaceutically acceptable adjuvant.

23 33. The extended-release galenical composition of Claim 31, wherein said salt is the hydrochloride salt.

34 34. The extended-release galenical composition of Claim 31, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

35 35. The extended-release galenical composition of Claim 31, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

36 36. The extended-release galenical composition of Claim 31, wherein the weight of the Diltiazem salt is about 20 to 95% by weight.

37 37. A pharmaceutical composition, comprising an extended-release galenical composition of Diltiazem or one or

23

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more pharmaceutically-acceptable salts thereof, which comprises in capsule form:

19 P. a) beads consisting essentially of an effective amount of each of Diltiazem or said one or more salts thereof and a wetting agent in admixture together, wherein said wetting agent is selected from the group consisting of a sugar, a  $C_{12}$ - $C_{20}$  fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide ester, an alcohol-polyglycide ester, lecithins and a combination thereof,

20 P. wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant, and

21 P. b) one or more other pharmaceutically active ingredients which are pharmaceutically compatible with Diltiazem or said one or more salts thereof.

22 37. The pharmaceutical composition of claim 36, wherein said one or more other pharmaceutically active ingredients

23 comprise  $\beta$ -adrenoceptor or diuretic compounds or compositions containing the same.

24 38. The pharmaceutical composition of claim 36, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

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98. The pharmaceutical composition of claim 36, wherein said salt is the hydrochloride salt.

99. The pharmaceutical composition of claim 38, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

100. A method for treating angina pectoris or hypertension or both in a mammal, which comprises administering to said mammal an effective amount of an extended-release galenical composition consisting essentially of Diltiazem or one or more pharmaceutically-acceptable salts thereof and a wetting agent in admixture together in the form of beads, wherein the wetting agent is selected from the group consisting of a sugar, a  $C_{12}$ - $C_{20}$  fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, an alcohol-polyglycide ester, a glyceride-polyglyceride lecithins and a combination thereof, and

101 wherein the beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable excipient.

102. The method of claim 101, wherein said administration is orally and once per day.

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13. ~~13~~ The method of claim ~~11~~, wherein said mammal is a human.

14. ~~14~~ The method of claim ~~12~~, wherein from about 120 mg to about 480 mg of said one or more Diltiazem salts are administered in total per day.

15. ~~15~~ The method of claim ~~11~~, wherein said salt is the hydrochloride salt.

16. An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient, each bead containing one or more of the Diltiazem salts and an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water, acid, and base insoluble polymer and a pharmaceutically-acceptable adjuvant.

17. The composition of Claim 16, wherein the wetting agent is selected from the group consisting of C<sub>12</sub>-C<sub>20</sub> fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of

*26* end

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polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins and a combination thereof.

48. The composition of Claim 46, wherein the wetting agent is sugar.

49. The composition of Claim 46, wherein the effective amount of the wetting agent is about 8% by weight of the composition.

50. The extended release galenical composition of Claim 32, wherein the wetting agent is sucrose stearate, the water-soluble or water-dispersible polymer or copolymer is hydroxypropylmethylcellulose and the water, acid and base insoluble polymer is an acrylic polymer.

#### REMARKS

Claims 12-30 have been cancelled. New Claims 31-50 have been added. Hence, Claims 31-50 are now active in this application.

#### REQUEST FOR RECONSIDERATION

Applicants wish to thank Examiner Spear for the recent helpful and courteous discussion conducted with their U.S. representative. In accordance with the remarks made during the discussion, Applicants have amended the claims to clarify the present invention. Now, in conjunction with and in addition to the remarks made during the discussion, Applicants

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wish to further distinguish the present invention from the cited references.

As noted previously, Diltiazem hydrochloride is used as a medicine primarily for its calcium channel blocking properties. Therefore, it finds application in the treatment of angina pectoris and hypertension.

Both angina pectoris and hypertension require continuous and constant control, however. Thus, Diltiazem must be administered every 6 to 8 hours as it has a very short half-life in blood of only about 3-4 hours. Unfortunately, such frequent administration times render Diltiazem administration very annoying or even impossible to effect, particularly during the night.

Although these drawbacks have been eliminated to some extent using a known galenic form of sustained-released Diltiazem, using this form still requires that the patient take the medication twice daily. Further, the process by which this product is prepared requires the use of organic solvents which are dangerous to use due to their flammability and toxicity, and which pose environmental hazards in their disposal.

In accordance with the present invention, however, a multiple unit extended-release Diltiazem galenical form is provided which need be administered only once daily. Moreover, the process by which this product is made does not use organic solvents.

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In particular, and in part, the present invention provides an extended-release galenical composition of Diltiazem or one or more pharmaceutically-acceptable salts thereof, which comprises beads, the beads consisting essentially of in admixture together:

- a) an effective amount of Diltiazem or said one or more salts thereof as an active ingredient, and
- b) an effective amount of a wetting agent, wherein said wetting agent is selected from the group consisting of a sugar, a  $C_{12}$ - $C_{20}$  fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester, lecithins and a combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl acrylate, and a pharmaceutically-acceptable adjuvant.

Thus, at the outset, it is noted that the present composition is characterized by the use of beads consisting essentially of in admixture together an effective amount of Diltiazem or one or more salts thereof as an active ingredient and the wetting agent as defined in the claims. The beads are also coated with a microporous membrane as defined in the claims.

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In essence, in admixture, the wetting agent appears to control, or strongly influence, the solubility of Diltiazem and does not permit this solubility to be affected by pH or other adverse conditions in the gastrointestinal tract. Further, this control appears to occur within the core of Diltiazem and wetting agent. This control affords a gradual release of Diltiazem in a relatively uniform manner over a period of about 24 hours.

Claims 12-16 and 22-26 stand rejected under 35 U.S.C. 102(e) as being anticipated by Debregeas et al. However, this reference neither discloses nor suggests the present invention.

In particular, from column 3, lines 3-31, of Debregeas et al., it is clear that the process thereof results in a compositional form having i) an 'core' of mutual excipient, which is described as a mixture of saccharose or fructose and starch, ii) an outer layer thereon of polyvinylpyrrolidone (PVP) and Diltiazem and iii) a coating thereon. Thus, in Debregeas et al., Diltiazem is in admixture with only PVP, and not with the "core" of that composition.

By contrast, the present formulation contains Diltiazem or one or more salts thereof in admixture together with the wetting agent. By combining the wetting agent in admixture with Diltiazem or one or more salts thereof, the solubility of the Diltiazem may be controlled and rendered independent of

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pH. This is quite important due to the wide variation in pH in the gastrointestinal tract.

In more detail, Debregeas et al describe a process which commences with a neutral core generally known as the "building-up" process. Pellets so obtained are coated with an organic solution of shellac and ethyl cellulose, or a dispersion of ethyl cellulose. Also, acrylic acid esters and methacrylic acid esters having a low content of quaternary ammonium groups may also be used with organic solvents such as lower alcohols, acetone and ethyl chloride. Hence, this process is representative of the conventional process which uses organic solvents. This is avoided by virtue of the present invention.

Furthermore, the "in vitro" release of products according to Debregeas et al is extremely dependent on the medium of conditions used for testing. Also, the "in vivo" performance of such a product is ascertainable only after a correlation of in vivo/in vitro has been established, if this is even possible. Debregeas et al discloses the use of the USP XXI method, as such a method of correlation.

However, after careful review of the USP XXI method, the, present inventors have not been able to find any method of dissolution for Diltiazem. In fact, Diltiazem is not even listed in USP XXI. Further, Annex II shows that Diltiazem was incorporated into USP XXII, which only became official on January 1, 1990, two years after Debregeas et al filed their

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application. Further, it was not until Supplement 6 became official in March of 1992 that the artisan could have found any method of dissolution for Diltiazem extended-release. Thus, Applicants must ask by what method was the dissolution data of Claim 1 of Debregeas et al generated? This is unclear, and, thus, without meaning.

Further, the galenical Diltiazem preparation described by Debregeas et al clearly does not disclose a Diltiazem bead composition containing a wetting agent, prepared by the extrusion spheronization process. Such a bead composition is necessarily a homogeneous bead composition. By contrast, the "building-up" process described by Debregeas et al is of no utility for the present invention as the present invention does not use the "building-up" process.

Furthermore, at column 7, line 65, Debregeas et al describes that:

. . . the microgranules can be prepared by extrusion followed by rounding.

No further description is given. In fact, such a procedure is impossible as microgranules of the type constituted by a central core as in Debregeas et al cannot be produced by the extrusion-spheronization process. By contrast, in accordance with the present invention, the extrusion-spheronization process leads to homogeneous type beads while the "building-up" process, starting with a sugar core, leads to heterogeneous type beads. Clearly, it is impossible to have a sugar central core in a homogeneous bead

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as in the present invention. Such a bead is, by nature, heterogeneous.

Further, the advantages of the present extrusion-spheronization process versus the building-up process of Debregeas et al may be noted as follows. Namely, for the present process:

- a) There is no need of a central core for "build-up",
- b) The present process is less time consuming: The building-up process of Debregeas et al requires between 50 and 200 layers to be applied successively and the preparation of each layer of requires:

- 1. Wetting the beads with a polymeric solution, wherein the solvent wets the beads and the polymer acts as a "glue",
- 2. Powdering with the substance, and
- 3. Drying the beads so as to evaporate completely all the solvents.

- c) The extrusion-spheronization process permits the use of water as solvent, without any drawbacks while in the building-up process the use of water increases dramatically the process time.

Further, the use of water as solvent in the present process has the following Advantages:

- 1. water is very inexpensive,
- 2. water is non-toxic and does not require complete removal from the pharmaceutical formulation and does not

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require special protection equipment for the operators during the process,

3. water is non-flammable. This drastically reduces the fire protection equipment needed during the process, and

4. water is the only environment friendly solvent. Because of the limitations on solvent emission in most countries worldwide, this process can be used practically everywhere.

d) Further, the extrusion-spheronization permits working in very large batches; the batch size is only dependent on the mixer size.

e) Finally, the extrusion-spheronization process can be adapted to the continuous production of beads.

Additionally, Debregeas et al neither describes nor suggests the use of an aqueous dispersion a neutral copolymer of ethylacrylate and methyl methacrylate (Eudragit NE30D) as in the present invention. The Eudragits described by Debregeas et al are copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups (Eudragit RS and RL) which can only be used in solutions with organic solvents. The environmental and toxicity concerns expressed in the present application are neither noted nor addressed by Debregeas et al.

Further, at column 3, lines 4 and 10, Debregeas et al describes the composition of the neutral core of saccharose and fructose to start the building-up process with the binder

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being polyvinylpyrrolidone to make the different layers of product. By contrast, the present invention does not use the building-up process and thus does not make use of a neutral core of saccharose and fructose. Further, Debregeas et al does not disclose saccharose as a wetting agent. The saccharose contained in the central core of the bead cannot act as a wetting agent because in order to do so the saccharose must be mixed with the Diltiazem and, therefore, saccharose must be in solution with Diltiazem. Unfortunately, in this system saccharose can only end up in solution after all the layers of Diltiazem are dissolved. In other words, saccharose can only become effective when there is no longer a need therefor.

The wetting agents claimed in the present invention are substances which are believed to modify the solubility of Diltiazem inside the coated beads when they are placed in a dissolution medium or when they are ingested by a mammal. This concept is neither disclosed nor suggested by Debregeas et al. Debregeas et al does not disclose a wetting agent- polyvinylpyrrolidone is not a wetting agent, it is a binder and plastifying agent. More specifically, Debregeas et al neither discloses nor suggest the use of any wetting agent, let alone those comprising a sugar, a  $C_{12}$  to  $C_{20}$  fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols or polyoxyethylene, an ester of sorbitan, an ester of

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polyoxyethylene sorbitan, a glyceride-polyglycides, an alcohol-polyglycide esters or lecithins, or any combination thereof.

In fact, since Debregeas et al fails either to disclose or suggest the use of any wetting agent, the teachings thereof would be of no use to the artisan in attempting to arrive at the present invention, which requires the use of wetting agents in order to obtain the observed properties of the present compositions.

Moreover, the product produced by Debregeas et al may be distinguished from the present product.

One in vivo parameter that permits one to estimate the performance of a sustained release product is the time of maximal concentration,  $T_{max}$ . The most significant values of  $T_{max}$  are obtained after multiple administrations.  $T_{max}$  measured after multiple administrations of the product of the present invention (see page 17) is  $8.0 \pm 1.8$  h. The  $T_{max}$  observed with Cardizen SR, a conventional product administered twice daily was  $5.2 \pm 2.8$  h. These data show clearly that the product of the present invention is much more adapted for administration once daily than that obtained by Debregeas et al. Moreover Debregeas et al obtain values of  $T_{max}$  which are somewhat lower but comparable to the ones obtained with Cardizen SR, which is a product designed and approved by the U.S. FDA for use.

As a further comparison, the following values are, again, noted:

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Debregeas patent: $T_{max}$ after multiple administrations [h]			
	TABLE II	TABLE IV	
Coating	Shellac Ethylcellulose	Shellac	Aquoat (Ethylcellulose dispersion)
180 mg	4.7		5.5
240 mg	4.95		
300 mg	6.6	4.2	3 - 5.6
Mean $T_{max}$ = $4.93 \pm 1.45$ h.			

Thus, the present compositions are not only clearly different from but surprisingly superior to those of Debregeas et al.

Notably, the  $T_{max}$  values recited above are comparable to those reported for Cardizen SR. This is not surprising, however, as Debregeas et al is representative of a conventional "building-up" process.

Furthermore, Applicants enclose herewith a Rule 132 Declaration which establishes several very important points.

First, the Declaration establishes that the "core" or "center" of the present composition is homogeneous with respect to Diltiazem and wetting agent.

In particular, Experiment 1 of the Declaration illustrates that in admixing for the amount of time shown, a homogeneous of Diltiazem and wetting agent is obtained, indicating that the mixture, itself, is homogeneous. The results of this are shown in the table at page 3 of the Declaration.

-17-

From Experiment 2 of the Declaration, it may be seen that the dissolution profile of an extended-release product is very dependent on the medium in which the test is performed. As Debregeas et al describes only an "aqueous medium", it is clear that any recitation of percent dissolved without defining the medium is meaningless.

Third, an experiment is provided in which an in vivo comparison of the present product is compared with two approved "once daily" products now available on the U.S. market. The results of this bioavailability study are shown in the last figure of the Declaration.

Thus, it is clear that there is a difference in the physical structure and chemical structure between the present compositions and those of Debregeas et al. Further, it is clear that the results of the present invention would be quite surprising to the artisan.

Accordingly, this ground of rejection is believed to be unsustainable and should be withdrawn.

Claims 27-30 stand rejected under 35 U.S.C. 103 as being unpatentable over Debregeas et al.

However, in view of all of the above, this ground of rejection is believed to be moot.

Claims 17-21 stand rejected under 35 U.S.C. 103 as being unpatentable over Debregeas et al in view of Yoshi. However, the latter reference fails to correct the deficiencies of the former cited reference.

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In particular, Joshi describes modified-release formulations in the form of extruded spheronized beadlets from which medicament is released at a controlled rate, the beadlets containing:

- a) from 3 to 60% of medicament,
- b) from 5 to 50% of an organic carboxylic acid, and
- c) non-lipophilic non fat binder, wherein
- d) said beadlets having a hardness of at least 2 strong cobbs units.

Joshi does not, however, describe or suggest an extended release formulation, although this is not the purpose of Joshi. The only word used in the disclosure is "modified release". However, no description is provided of any sustained release properties, such as in vitro or in vivo data. It is submitted that this is because no such properties exist for these compositions. For example, if example 9 is considered, which relates to a Diltiazem formulation the composition is:

CONSTITUENT	PARTS BY WEIGHT
Diltiazem	20
Citric acid	30
Microcrystalline cellulose	43
TOTAL	93

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This formulation will be relatively hygroscopic due to the high citric acid content and the Diltiazem from these beads will be released extremely fast. In water, for example, not more than 30 minutes would be required to release at least 80% of the Diltiazem. However, this is exactly what the artisan would do in order to obtain an extremely fast Diltiazem release formulation!

It is known by the artisan, that every sustained release drug is a new system by itself. This is due to the very large number of parameters which must be taken in consideration such as: physico-chemical properties, i.e. solubility, crystallinity, pH, pKa, etc.; pharmacokinetical properties, i.e. absorption, distribution, metabolism, first pass effect, elimination, recirculation, efficacy and toxicity limits, etc.; and medical properties, i.e. effect of drug, effect of metabolites, side-effects, shape of clinically desired blood concentrations profiles, etc. Joshi cites a list of drugs from column 8, line 40 to column 9, line 20; i.e., about 130 different products. This is simply a product listing wherein products appear such as: "basic salts like alkali metal salts". However, this would be of no help to the artisan as when mixed with organic carboxylic acids in water, such salts would undergo a neutralization reaction.

In fact, the present invention does not use organic carboxylic acids therein, whereas in the Joshi process this is essential. See column 9, lines 52-54 and Claim 1. Moreover,

-20-

Joshi does not disclose the use of a "wetting agent" in the uncoated beads manufacturing process. Further, Joshi does not disclose the characteristics of the obtained products and, therefore, one skilled in the art would be unable to know or to understand the advantages and the limits of this patent.

Hence, this ground of rejection is also believed to be unsustainable and should be withdrawn.

In summary, inasmuch as both cited references prepare a product by a method different from the present invention, and inasmuch as these processes are incompatible with the present process and further inasmuch as the present product is distinguishable in at least one property over that of Debregeas et al, it is believed that each claimed aspect of the present invention is fully patentable over the cited references.

The specification stands objected to under 35 USC 112, first paragraph.

However, in view of the above amendments, this ground of rejection is believed to be moot.

Finally, it is believed clear that all recitations of "uncoated beads" in the dependant Claims have antecedent basis in the recitation of "beads" in the independent Claims. This is believed to be clear as each of the independent Claims has a separate reference therein to a coating, making it clear that the "beads" are apart from the coating and, in fact, have

-21-

a coating ~~thereon~~. Thus, the reference to "beads" is to  
uncoated beads.

Accordingly, in view of all of the above amendments and  
attendant remarks, it is believed that the present application  
now stands in condition for allowance. Early notice to this  
effect is earnestly solicited.

Respectfully submitted,

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# EXHIBIT 5

4040-002-10 CONT



IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :  
ARTHUR M. DEBOECK ET AL : GROUP ART UNIT: 1502  
SERIAL NO: NEW APPLICATION :  
FILED: HEREWITH : EXAMINER: SPEAR  
FCR: EXTENDED RELEASE FORM  
OF DILTIAZEM

PRELIMINARY AMENDMENT

HONORABLE COMMISSIONER OF PATENTS & TRADEMARKS  
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend this  
application as follows.

IN THE CLAIMS

Please cancel Claims 1-11 without prejudice and insert  
therefor the following new claims:

- B
- 12. An extended-release galenical composition of  
Diltiazem or one or more pharmaceutically-acceptable salts  
thereof, which comprises beads, said beads consisting  
essentially of in admixture together:
- a) an effective amount of Diltiazem or said one or more  
salts thereof as an active ingredient, and
  - b) an effective amount of a wetting agent, wherein said  
wetting agent is selected from the group consisting of a  
sugar, a C<sub>12</sub>-C<sub>20</sub> fatty acid ester of sucrose or xylose, a

-2-

glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester, lecithins and a combination thereof,

*3, cont*  
 wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl acrylate, and a pharmaceutically-acceptable adjuvant.

13. The extended-release galenical composition of Claim 12, wherein said salt is the hydrochloride salt.

14. The extended-release galenical composition of Claim 13, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

15. The extended-release galenical composition of Claim 12, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

16. The extended-release galenical composition of Claim 12, wherein the weight of the Diltiazem salt is about 20 to 95% by weight.

17. A pharmaceutical composition, comprising an extended-release galenical composition of Diltiazem or one or more pharmaceutically-acceptable salts thereof, which comprises in capsule form:

a) beads consisting essentially of an effective amount of each of Diltiazem or said one or more salts thereof and a

-3-

*B;  
cont.*

wetting agent in admixture together, wherein said wetting agent is selected from the group consisting of a sugar, a C<sub>2</sub>-C<sub>20</sub> fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide ester, an alcohol-polyglycide ester, lecithins and a combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant, and

b) one or more other pharmaceutically active ingredients which are pharmaceutically compatible with Diltiazem or said one or more salts thereof.

18. The pharmaceutical composition of Claim 16, wherein said one or more other pharmaceutically active ingredients comprise  $\beta$ -adrenoceptor or diuretic compounds or compositions containing the same.

19. The pharmaceutical composition of Claim 16, wherein the weight of the microporous membrane is about 2 to 15% by weight of that of the uncoated beads.

20. The pharmaceutical composition of Claim 16, wherein said salt is the hydrochloride salt.

-4-

21. The pharmaceutical composition of Claim 16, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

B' cont  
22. A method for treating angina pectoris or hypertension or both in a mammal, which comprises administering to said mammal an effective amount of an extended-release galenical composition consisting essentially of Diltiazem or one or more pharmaceutically-acceptable salts thereof and a wetting agent in admixture together in the form of beads, wherein the wetting agent is selected from the group consisting of a sugar, a C<sub>12</sub>-C<sub>20</sub> fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, an alcohol-polyglycide ester, a glyceride-polyglyceride lecithins and a combination thereof, and

wherein the beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable excipient.

23. The method of Claim 21, wherein said administration is orally and once per day.

24. The method of Claim 21, wherein said mammal is a human.

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25. The method of Claim 22, wherein from about 120 mg to about 480 mg of said one or more Diltiazem salts are administered in total per day.

26. The method of Claim 21, wherein said salt is the hydrochloride salt.

27. An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient, each bead containing one or more of the Diltiazem salts and an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water, acid, and base insoluble polymer and a pharmaceutically-acceptable adjuvant.

28. The composition of Claim 26, wherein the wetting agent is selected from the group consisting of C<sub>12</sub>-C<sub>20</sub> fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins and a combination thereof.

B.  
Cont

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29. The composition of Claim 26, wherein the wetting agent is sugar.

B1  
Cont

30. The composition of Claim 26, wherein the effective amount of the wetting agent is about 1% by weight of the composition.

31. The extended release galenic composition of Claim 22, wherein the wetting agent is sucrose stearate, the water-soluble or water-dispersible polymer or copolymer is hydroxypropylmethylcellulose and the water, acid and base insoluble polymer is an acrylic polymer.--

#### REMARKS

Claims 1-11 have been cancelled. New Claims 12-31 have been added. Hence, Claims 12-31 are now active in this application.

#### PRELIMINARY REMARKS

Applicants have amended the Claims to clarify the present invention. All of the above amendments are fully supported by the disclosure and Claims as originally filed.

Applicants now wish to make the following remarks.

Both angina pectoris and hypertension require continuous and constant control, however. Thus, Diltiazem must be administered every 6 to 8 hours as it has a very short half-life in blood of only about 3-4 hours. Unfortunately, such frequent administration times render Diltiazem administration

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very annoying or even impossible to effect, particularly during the night.

Although these drawbacks have been eliminated to some extent using a known galenic form of sustained-released Diltiazem, using this form still requires that the patient take the medication twice daily. Further, the process by which this product is prepared requires the use of organic solvents which are dangerous to use due to their flammability and toxicity, and which pose environmental hazards in their disposal.

In accordance with the present invention, however, a multiple unit extended-release Diltiazem galenical form is provided which need be administered only once daily. Moreover, the process by which this product is made does not use organic solvents.

In particular, and in part, the present invention provides an extended-release galenical composition of Diltiazem or one or more pharmaceutically-acceptable salts thereof, which comprises beads, the beads consisting essentially of in admixture together:

a) an effective amount of Diltiazem or said one or more salts thereof as an active ingredient, and

b) an effective amount of a wetting agent, wherein said wetting agent is selected from the group consisting of a sugar, a  $C_{12}$ - $C_{20}$  fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene,

-U-

an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester, lecithins and a combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl acrylate, and a pharmaceutically-acceptable adjuvant.

Thus, at the outset, it is noted that the present composition is characterized by the use of beads consisting essentially of in admixture together an effective amount of Diltiazem or one or more salts thereof as an active ingredient and the wetting agent as defined in the claims. The beads are also coated with a microporous membrane as defined in the claims.

In essence, in admixture, the wetting agent appears to control, or strongly influence, the solubility of Diltiazem and does not permit this solubility to be affected by pH or other adverse conditions in the gastrointestinal tract. Further, this control appears to occur within the core of Diltiazem and wetting agent. This control affords a gradual release of Diltiazem in a relatively uniform manner over a period of about 24 hours. Further, the system of the present invention, as noted in the parent application, is quite different from that of Debregeas et al.

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In particular, from column 3, lines 3-31, of Debregeas et al., it is clear that the process thereof results in a compositional form having i) an 'core' of mutual excipient, which is described as a mixture of saccharose or fructose and starch, ii) an outer layer thereon of polyvinylpyrrolidone (PVP) and Diltiazem and iii) a coating thereon. Thus, in Debregeas et al., Diltiazem is in admixture with only PVP, and not with the "core" of that composition.

By contrast, the present formulation contains Diltiazem or one or more salts thereof in admixture together with the wetting agent. By combining the wetting agent in admixture with Diltiazem or one or more salts thereof, the solubility of the Diltiazem may be controlled and rendered independent of pH. This is quite important due to the wide variation in pH in the gastrointestinal tract.

In more detail, Debregeas et al. describe a process which commences with a neutral core generally known as the "building-up" process. Pellets so obtained are coated with an organic solution of shellac and ethyl cellulose, or a dispersion of ethyl cellulose. Also, acrylic acid esters and methacrylic acid esters having a low content of quaternary ammonium groups may also be used with organic solvents such as lower alcohols, acetone and ethyl chloride. Hence, this process is representative of the conventional process which uses organic solvents. This is avoided by virtue of the present invention.

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Furthermore, the "in vitro" release of products according to Debregeas et al is extremely dependent on the medium of conditions used for testing. Also, the "in vivo" performance of such a product is ascertainable only after a correlation of in vivo/in vitro has been established, if this is even possible. Debregeas et al discloses the use of the USP XXI method, as such a method of correlation.

However, after careful review of the USP XXI method, the, present inventors have not been able to find any method of dissolution for Diltiazem. In fact, Diltiazem is not even listed in USP XXI. Further, Annex II shows that Diltiazem was incorporated into USP XXII, which only became official on January 1, 1990, two years after Debregeas et al filed their application. Further, it was not until Supplement 5 became official in March of 1992 that the artisan could have found any method of dissolution for Diltiazem extended-release. Thus, Applicants must ask by what method was the dissolution data of Claim 1 of Debregeas et al generated? This is unclear, and, thus, without meaning.

Further, the galenical Diltiazem preparation described by Debregeas et al clearly does not disclose a Diltiazem bead composition containing a wetting agent, prepared by the extrusion spheronization process. Such a bead composition is necessarily a homogeneous bead composition. By contrast, the "building-up" process described by Debregeas et al is of no

-11-

utility for the present invention as the present invention does not use the "building-up" process.

Furthermore, at column 7, line 65, Debregeas et al describes that:

. . . the microgranules can be prepared by extrusion followed by rounding.

No further description is given. In fact, such a procedure is impossible as microgranules of the type constituted by a central core as in Debregeas et al cannot be produced by the extrusion-spheronization process. By contrast, in accordance with the present invention, the extrusion-spheronization process leads to homogeneous type beads while the "building-up" process, starting with a sugar core, leads to heterogeneous type beads. Clearly, it is impossible to have a sugar central core in a homogeneous bead as in the present invention. Such a bead is, by nature, heterogeneous.

Further, the advantages of the present extrusion-spheronization process versus the building-up process of Debregeas et al may be noted as follows. Namely, for the present process:

- a) There is no need of a central core for "build-up",
- b) The present process is less time consuming: The building-up process of Debregeas et al requires between 50 and 200 layers to be applied successively and the preparation of each layer of requires:

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1. Wetting the beads with a polymeric solution, wherein the solvent wets the beads and the polymer acts as a "glue",
2. Powdering with the substance, and
3. Drying the beads so as to evaporate completely all the solvents.

c) The extrusion-spheronization process permits the use of water as solvent, without any drawbacks while in the building-up process the use of water increases dramatically the process time.

Further, the use of water as solvent in the present process has the following Advantages:

1. water is very inexpensive,
2. water is non-toxic and does not require complete removal from the pharmaceutical formulation and does not require special protection equipment for the operators during the process,
3. water is non-flammable. This drastically reduces the fire protection equipment needed during the process, and
4. water is the only environment friendly solvent.

Because of the limitations on solvent emission in most countries worldwide, this process can be used practically everywhere.

d) Further, the extrusion-spheronization permits working in very large batches; the batch size is only dependent on the mixer size.

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e) Finally, the extrusion-spheronization process can be adapted to the continuous production of beads.

Additionally, Debregeas et al neither describes nor suggests the use of an aqueous dispersion a neutral copolymer of ethylacrylate and methyl methacrylate (Eudragit NE300) as in the present invention. The Eudragits described by Debregeas et al are copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups (Eudragit RS and RL) which can only be used in solutions with organic solvents. The environmental and toxicity concerns expressed in the present application are neither noted nor addressed by Debregeas et al.

Further, at column 3, lines 4 and 10, Debregeas et al describes the composition of the neutral core of saccharose and fructose to start the building-up process with the binder being polyvinylpyrrolidone to make the different layers of product. By contrast, the present invention does not use the building-up process and thus does not make use of a neutral core of saccharose and fructose. Further, Debregeas et al does not disclose saccharose as a wetting agent. The saccharose contained in the central core of the bead cannot act as a wetting agent because in order to do so the saccharose must be mixed with the Diltiazem and, therefore, saccharose must be in solution with Diltiazem. Unfortunately, in this system saccharose can only end up in solution after all the layers of Diltiazem are dissolved. In other words,

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saccharose can only become effective when there is not longer a need therefor.

The wetting agents claimed in the present invention are substances which are believed to modify the solubility of Diltiazem inside the coated beads when they are placed in a dissolution medium or when they are ingested by a mammal. This concept is neither disclosed nor suggested by Debregeas et al. Debregeas et al does not disclose a wetting agent- polyvinylpyrrolidone is not a wetting agent, it is a binder and plastifying agent. More specifically, Debregeas et al neither discloses nor suggest the use of any wetting agent, let alone those comprising a sugar, a  $C_{12}$  to  $C_{20}$  fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols an polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycides, an alcohol-polyglycide esters or lecithins, or any combination thereof.

In fact, since Debregeas et al fails either to disclose or suggest the use of any wetting agent, the teachings thereof would be of no use to the artisan in attempting to arrive at the present invention, which requires the use of wetting agents in order to obtain the observed properties of the present compositions.

Moreover, the product produced by Debregeas et al may be distinguished from the present product.

A-77

-15-

One in vivo parameter that permits one to estimate the performance of a sustained release product is the time of maximal concentration,  $T_{max}$ . The most significant values of  $T_{max}$  are obtained after multiple administrations.  $T_{max}$  measured after multiple administrations of the product of the present invention (see page 17) is  $8.0 \pm 1.8$  h. The  $T_{max}$  observed with Cardizen SR, a conventional product administered twice daily was  $5.2 \pm 2.8$  h. These data show clearly that the product of the present invention is much more adapted for administration once daily than that obtained by Debregeas et al. Moreover Debregeas et al obtain values of  $T_{max}$  which are somewhat lower but comparable to the ones obtained with Cardizen SR, which is a product designed and approved by the U.S. FDA for use.

As a further comparison, the following values are, again, noted:

Debregeas patent: $T_{max}$ after multiple administrations			
[h]			
	TABLE II	TABLE IV	
Coating	Shellac Ethylcellulose	Shellac	Aquoat (Ethylcellulose dispersion)
180 mg	4.7		5.5
240 mg	4.95		
300 mg	6.6	4.2	3 - 5.6
Mean $T_{max} = 4.93 \pm 1.45$ h.			

-16-

Thus, the present compositions are not only clearly different from but surprisingly superior to those of Debregeas et al.

Notably, the  $T_{max}$  values recited above are comparable to those reported for Cardizen SR. This is not surprising, however, as Debregeas et al is representative of a conventional "building-up" process.

Furthermore, Applicants submitted in the parent application a Rule 132 Declaration which establishes several very important points.

First, the Declaration establishes that the "core" or "center" of the present composition is homogeneous with respect to Diltiazem and wetting agent.

In particular, Experiment 1 of the Declaration illustrates that in admixing for the amount of time shown, a homogeneous of Diltiazem and wetting agent is obtained, indicating that the mixture, itself, is homogeneous. The results of this are shown in the table at page 3 of the Declaration.

From Experiment 2 of the Declaration, it may be seen that the dissolution profile of an extended-release product is very dependent on the medium in which the test is performed. As Debregeas et al describes only an "aqueous medium", it is clear that any recitation of percent dissolved without defining the medium is meaningless.

-17-

Third, an experiment is provided in which an in vivo comparison of the present product is compared with two approved "once daily" products now available on the U.S. market. The results of this bioavailability study are shown in the last figure of the Declaration.

Thus, it is clear that there is a difference in the physical structure and chemical structure between the present compositions and those of Debregeas et al. Further, it is clear that the results of the present invention would be quite surprising to the artisan.

The present invention, as noted in the parent case, is also readily distinguishable from Joshi.

In particular, Joshi describes modified-release formulations in the form of extruded spheronized beadlets from which medicament is released at a controlled rate, the beadlets containing:

- a) from 3 to 60% of medicament,
- b) from 5 to 50% of an organic carboxylic acid, and
- c) non-lipophilic non fat binder, wherein
- d) said beadlets having a hardness of at least 2 strong cobbs units.

Joshi does not, however, describe or suggest an extended release formulation, although this is not the purpose of Joshi. The only word used in the disclosure is "modified release". However, no description is provided of any sustained release properties, such as in vitro or in vivo

-18-

data. It is submitted that this is because no such properties exist for these compositions. For example, if example 9 is considered, which relates to a Diltiazem formulation the composition is:

CONSTITUENT	PARTS BY WEIGHT
Diltiazem	20
Citric acid	30
Microcrystalline cellulose	43
TOTAL	93

This formulation will be relatively hygroscopic due to the high citric acid content and the Diltiazem from these beads will be released extremely fast. In water, for example, not more than 30 minutes would be required to release at least 80% of the Diltiazem. However, this is exactly what the artisan would do in order to obtain an extremely fast Diltiazem release formulation!

It is known by the artisan, that every sustained release drug is a new system by itself. This is due to the very large number of parameters which must be taken in consideration such as: physico-chemical properties, i.e. solubility, crystallinity, pH, pKa, etc.; pharmacokinetical properties, i.e. absorption, distribution, metabolization, first pass effect, elimination, recirculation, efficacy and toxicity limits, etc.; and medical properties, i.e. effect of drug,

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effect of metabolites, side-effects, shape of clinically desired blood concentrations profiles, etc. Joshi cites a list of drugs from column 8, line 40 to column 9, line 20; i.e., about 130 different products. This is simply a product listing wherein products appear such as: "basic salts like alkali metal salts". However, this would be of no help to the artisan as when mixed with organic carboxylic acids in water, such salts would undergo a neutralization reaction.

In fact, the present invention does not use organic carboxylic acids therein, whereas in the Joshi process this is essential. See column 9, lines 52-54 and Claim 1. Moreover, Joshi does not disclose the use of a "wetting agent" in the uncoated beads manufacturing process. Further, Joshi does not disclose the characteristics of the obtained products and, therefore, one skilled in the art would be unable to know or to understand the advantages and the limits of this patent.

In summary, inasmuch as both cited references prepare a product by a method different from the present invention, and inasmuch as these processes are incompatible with the present process and further inasmuch as the present product is distinguishable in at least one property over that of Debregeas et al, it is believed that each claimed aspect of the present invention is fully patentable over the cited references.

Finally, it is believed clear that all recitations of "uncoated beads" in the dependant Claims have antecedent basis

-20-

in the recitation of "beads" in the independent claims. This is believed to be clear as each of the independent claims has a separate reference therein to a coating, making it clear that the "beads" are apart from the coating and, in fact, have a coating thereon. Thus, the reference to "beads" is to uncoated beads.

Accordingly, in view of all of the above amendments and attendant remarks, it is believed that the present application is now in condition for examination on the merits. Favorable consideration is earnestly solicited.

Respectfully submitted,

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# EXHIBIT 6

4040-002-10 FWC

RESPONSE UNDER 37 C.F.R. §1.116 -  
EXPEDITED PROCEDURE EXAMINING GROUP 1502

IN THE UNITED STATES PATENT & TRADEMARK OFFICE



APPLICATION OF: :  
ARTHUR M. DEBOECK ET AL : GROUP ART UNIT: 1502  
SERIAL NO: 08/311,722 :  
FILED: SEPTEMBER 23, 1994 : EXAMINER: SPEAR  
FOR: EXTENDED RELEASE FORM :  
OF DILTIAZEM

AMENDMENT UNDER 37 C.F.R. §1.116

ASSISTANT COMMISSIONER FOR PATENTS  
WASHINGTON, D.C. 20231

SIR:

Responsive to the Official Action of February 14, 1995 in  
the above-identified application, reconsideration is  
respectfully requested.

IN THE CLAIMS

Please cancel Claims 12-31 without prejudice and insert  
therefor the following new claims:

1. An extended-release galenical composition of one  
or more pharmaceutically-acceptable salts of Diltiazem which  
comprises beads containing an effective amount of one or more  
of said Diltiazem salts as the active ingredient, each bead  
containing one or more of the Diltiazem salts and an effective  
amount of a wetting agent in admixture with the one or more  
Diltiazem salts to maintain the solubility of the Diltiazem .n

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each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water-, acid- and base-insoluble polymer and a pharmaceutically-acceptable adjuvant,

and wherein the wetting agent is selected from the group consisting of sugars,  $C_{12}$ - $C_{20}$  fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins and a combination thereof.

2. The composition of Claim 1, wherein the wetting agent is a sugar.

3. The composition of Claim 1, wherein the effective amount of the wetting agent is about 8% by weight of the composition.

4. The composition of Claim 1, wherein the wetting agent is sucrose stearate, the water-soluble or water-dispersible polymer or copolymer is hydroxypropyl methylcellulose and the water, acid- and base-insoluble polymer is an acrylic polymer.

12-22-58

24

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REMARKS

Claims 12-31 have been cancelled. New Claims 32-35 have been added. Hence, Claims 32-35 are now active in this application.

REQUEST FOR RECONSIDERATION

Diltiazem hydrochloride is used in medicine principally for its calcium channel blocking properties, and, therefore, finds application in the treatment of angina pectoris and hypertension; either alone or in combination with other medications.

For illnesses which require continuous and constant control, such as hypertension and angina pectoris, however, Diltiazem must be administered every 6 to 8 hours, as it has a very short half-life in blood of only about 3 to 4 hours. However, such frequent administration times makes the treatment either quite annoying or even impossible to effect, especially at night. Moreover, after each administration of an immediate-release galenic form of Diltiazem, which is generally necessary four times per day, a succession of rapidly increasing and decreasing plasmatic Diltiazem concentrations are established. Thus, the organism being treated and the target organ, more particularly the heart, are alternatively subjected to overdoses and to underdoses of medicine. Although a sustained-release of form of Diltiazem

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is known (See U.S. 4,721,619) the patient is still obliged to take the medication twice daily. Moreover, for this formulation, a solvent is required to prepare a polymer solution in order to build-up between 20 and 40 layers of coating around the active ingredient. Solvents so used are methanol, isopropanol, acetone and methylene chloride which are both dangerous to use due to their flammability as well as their toxicity.

In accordance with the present invention, an extended-release diltiazem hydrochloride galenical form is provided which need be administered only once daily, and from which blood Diltiazem concentrations are not effected by the concomitant intake of food. Moreover, the present composition can be made by a process which does not use organic solvents.

In particular, the present invention provides an extended-release galenic composition of one or more pharmaceutically acceptable salts of Diltiazem which contains beads containing an effective amount of one or more of the Diltiazem salts as the active ingredient, each bead containing one or more of Diltiazem salts and an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastro-intestinal tract or other adverse conditions which the composition will meet therein, the beads being coated with a microporous membrane containing

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at least a water-soluble or water-dispersible polymer or copolymer, and a water-acid- and base-insoluble polymer and a pharmacologically-acceptable adjuvant,

wherein the wetting agent is selected from the group consisting of sugars,  $C_{12}$ - $C_{20}$  fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, glyceride-polyglycides, lecithins and a combination thereof.

Claim 27 stands rejected under 35 U.S.C. §102(a) as being anticipated by Carli et al '824.

However, it is quite clear that this reference fails to either disclose or suggest the present invention.

Notably, this reference fails to either disclose or suggest the present extended-release galenical composition of Diltiazem salts containing beads, each bead containing one or more of the Diltiazem salts and an effective amount of the present wetting agents, which is coated with a microporous membrane containing at least a water-soluble or water-dispersible polymer or copolymer and a water-, acid- and base-insoluble polymer and a pharmaceutically-acceptable adjuvant.

This particular combination is important as it ensures that the solubility of the active ingredient Diltiazem is unaffected by the pH of the gastrointestinal tract. This affords excellent bioavailability while avoiding plasmatic concentration peaks.

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Attached to this response are Figures 1 and 2 of the present specification.

Figure 1 clearly illustrates the gradual release of Diltiazem, according to the present invention, in a uniform manner over a period of about one day after the 8th day of twice daily administration.

Figure 2 clearly illustrates the effectiveness of the present composition with the concomitant ingestion of food. The solid curve represents mean plasma drug levels when the present composition is taken without food. The dotted curve represents mean plasma drug levels when the present composition is taken with food.

Clearly, the teachings of the cited reference would not place the present invention in the possession of the artisan. Likewise, there is nothing in this reference which would have rendered the present invention, as a whole, obvious at time the present invention was made.

However, in view of the above amendments, this ground of rejection is believed to be moot.

Claims 23-34, 26 and 28-31 stand rejected under 35 U.S.C. §112, fourth paragraph.

However, in view of the above amendments, this ground of rejection is believed to be moot.

Claims 12-22 and 25 stand rejected under 35 U.S.C. §101 as claiming the same invention as that of Claims 1-11 and 14 of U.S. 5,288,505.

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However, in view of the above-amendments, this ground of rejection is believed to be moot.

Accordingly, in view of all of the above amendments and attendant remarks, it is believed that the present application now stands in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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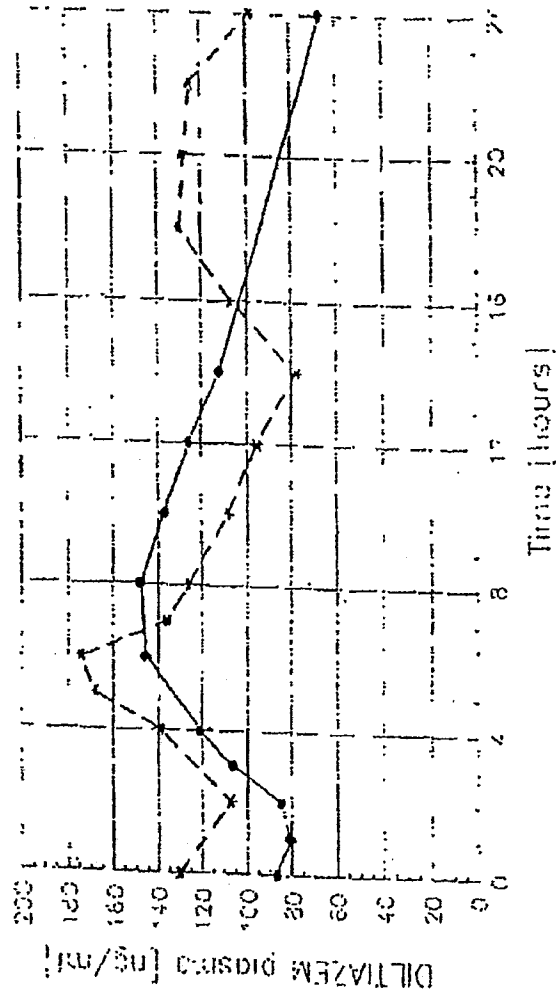


FIG 1

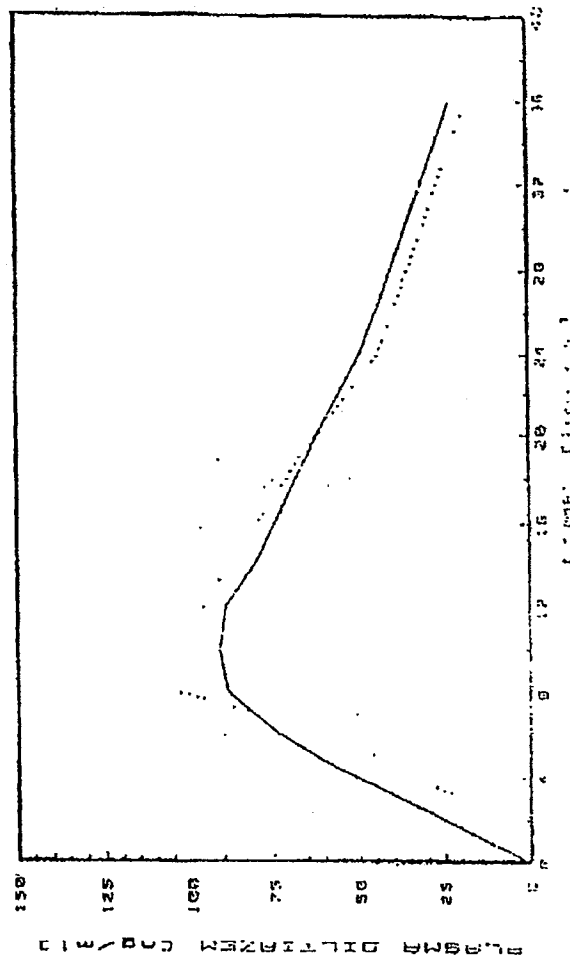
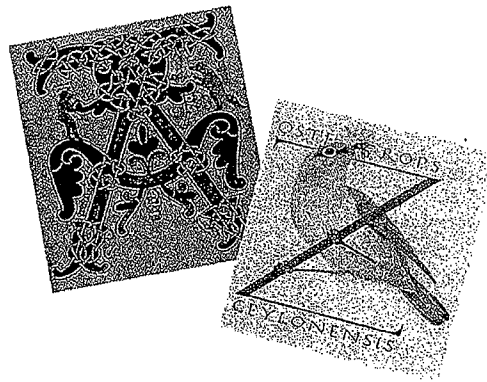


FIG 2

# EXHIBIT 7

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**American  
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*of the English Language*

FOURTH EDITION



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Manufactured in the United States of America

## homestead law | homologue

ownership of a 160-acre tract of public land to a citizen or a family who had resided on and cultivated the land for five years.

**stead law** *n.* Any of several laws passed in most states extending a homestead from attachment or forced sale to a homestead.

**stretch** (*hōm'strēch'*) *n.* 1. The portion of a racetrack from the start to the finish line. 2. Informal The final stages of an undertaking.

**study** *n.* A course of study in which instruction is offered at a school or university.

**style** (*hōm'stīl'*) *adj.* Prepared or served as if in the home: a home-style dish.

**theater** *n.* A system of sophisticated electronic equipment for the presentation of theater-quality images and sound in the home.

**town** (*hōm'taun'*) *n.* The town or city of one's birth, rearing, or residence.

**truth** *n.* A key or basic truth, especially one that is discovered or acknowledged.

**video** *n.* 1. A videotape that has been recorded on a personal video recorder. 2. The business of providing videotapes for viewing.

**ward** (*hōm'wārd'*) *adv. & adj.* Toward or at home. —**home-** (*hōm'*) *adv.*

**work** (*hōm'wōrk'*) *n.* 1. Work, such as schoolwork or piece-work, done at home. 2. Preparatory or preliminary work: did their work before coming to the meeting.

**ey** also **hom** (*hō'mē'*) *adj. -ier, -iest* Informal Having a home; comfortable; cozy. —**home/ey** *ness* *n.*

**ey** (*hō'mē'*) *n.* Slang A homeboy or homegirl.

**homicidal** (*hōm'i-sīd'l, hō'mī-*) *adj.* 1. Of or relating to homicide. 2. Capable of or conducive to homicide: a homicidal rage. —**homicide** (*hōm'i-sīd', hō'mī-*) *n.* 1. The killing of one person by another. 2. A person who kills another person. [Middle English, from Latin *homicidium* and *homicida*: *homo*, man; see *in* in Appendix I + *-cidium* and *-cida*, *-cide*.]

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hancing blood clotting. [*homo-*, homologous with (from HOMOLOGOUS) + CYSTEINE.]

**homoeocious** (*hō-mē'shās, hō-*) *adj.* Of or being a parasite that spends all stages of its life cycle on the same host. [HOMO- + Greek *oikia*, house; see HETEROECIOUS + -OUS.]

**Homo erectus** (*hō'mō ī-rēk'təs*) *n.* An extinct species of humans, regarded as an ancestor of *Homo sapiens*. [New Latin *Homō erectus*, species name: Latin *homō*, man + Latin *erectus*, upright.]

**homoeoretic** (*hō'mō-ī-rōt'ik*) *adj.* 1. Of or concerning homosexual love and desire. 2. Tending to arouse such desire.

**homoeoreticism** (*hō'mō-ī-rōt'ī-sīz'əm*) also **homoeoretism** (*-ēz'is*) *n.* A homoerotic quality or theme.

**homogametetic** (*hō'mō-gā-mēt'ik*) *adj.* Producing gametes that contain only one type of sex chromosome.

**homogamous** (*hō-mōg'a-məs*) *adj.* 1. Having one kind of flower on the same plant. 2. Having stamens and pistils that mature simultaneously.

**homogenate** (*hō-mōj'a-nāt', -nīt, hō-*) *n.* Something that has been homogenized. [HOMOGEN(IZE) + -ATE.]

**homogeneity** (*hō'mā-jā-nē-tē, -nā', hōm'a-*) *n., pl. -ties* The state or quality of being homogeneous.

**homogeneous** (*hō'mā-jē-nē-əs, -jēn'yəs*) *adj.* 1. Of the same or similar nature or kind: "a tight-knit, homogeneous society" (James Fallows). 2. Uniform in structure or composition throughout. 3. Mathematics Consisting of terms of the same degree or elements of the same dimension. [From Medieval Latin *homogeneus*, from Greek *homogenēs*: *homo-*, homo- + *genos*, kind; see HETEROGENEOUS.] —**homogeneously** *adv.* —**homogeneity** *n.*

**homogenize** (*hō-mōj'a-nīz', hō-*) *v. -nized, -nizing, -nizes* —*tr.* 1. To make homogeneous. 2a. To reduce to particles and disperse throughout a fluid. b. To make uniform in consistency, especially to render (milk) uniform in consistency by emulsifying the fat content. —*intr.* To become homogenized. [From HOMOGENOUS.] —**homogenization** (*-nī-zā'shən*) *n.* —**homogenizer** *n.*

**homogenous** (*hō-mōj'a-nəs, hō-*) *adj.* Of or exhibiting homogeneity.

**homogenous** (*hō-mōj'a-nəs, hō-*) *adj.* Homogeneous. [Alteration of HOMOGENEOUS (probably influenced by HOMOGENIZE).]

**homogeneity** (*hō-mōj'a-nē, hō-*) *n., pl. -nities* Similarity of structure between organs or parts, possibly of dissimilar function, that are related by common descent. [Greek *homogeneia*, community of origin, from *homogenēs*, of the same race, family, kind. See HOMOGENEOUS.]

**homograft** (*hō'mā-grāft', hōm'a-*) *n.* See **allograft**.

**homograph** (*hōm'a-grāf', hōm'a-*) *n.* One of two or more words that have the same spelling but differ in origin, meaning, and sometimes pronunciation, such as *fair* (pleasing in appearance) and *fair* (market) or *wind* (wind) and *wind* (wind). —**homographic** *adj.*

**Homo habilis** (*hāb'is-lās*) *n.* An extinct species of humans considered to be an ancestor of modern humans and the earliest hominid to make tools. This species existed between 1.5 and 2.0 million years ago. [New Latin *Homō habilis*, species name: Latin *homō*, man + Latin *habilis*, skillful.]

**homoi-** *pref.* Variant of **homeo-**.

**homoiotherm** (*hō-moi'ō-thūrm'*) *n.* Variant of **homeotherm**.

**Homoiou-sian** (*hō-moi'ō-sē-ən, -zē-*) *n.* A member of the Semi-Arian party in the fourth century A.D. that held that Jesus the Son and God the Father were of similar but not of the same substance. [From Greek *homoiou-sios*, of similar substance: *homoiō-*, homeo- + *ousiā*, substance (from *ousa*, feminine present participle of *einai*, to be; see *es-* in Appendix I).]

**homolecithal** (*hō'mō-lēs'ā-thəl*) *adj.* Having a yolk that is evenly distributed throughout: a homolecithal egg. [HOMO- + Greek *lekithos*, egg yolk + -AL.]

**homolog** (*hōm'a-lōg', -lōg', hōm'a-*) *n.* Variant of **homologue**.

**homologate** (*hō-mōl'a-gāt', hō-*) *tr.v. -gated, -gating, -gates* To approve, especially to confirm officially. [Medieval Latin *homologāre*, *homologāt-*, from Greek *homologeō*, to agree, from *homologos*, agreeing. See HOMOLOGOUS.] —**homologation** *n.*

**homological** (*hō'mā-lōj'ī-kəl, hōm'a-*) also **homologistic** (*-lōj'ik*) *adj.* Homologous. —**homologically** *adv.*

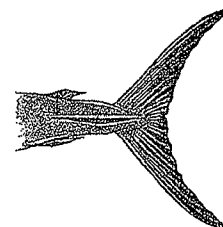
**homologize** (*hō-mōl'a-jīz', hō-*) *tr.v. -gized, -gizing, -gizes* 1. To make homologous. 2. To show to be homologous. —**homologization** (*-jīz'is*) *n.*

**homologous** (*hō-mōl'a-gəs, hō-*) *adj.* 1. Corresponding or similar in position, value, structure, or function. 2. Biology Similar in structure and evolutionary origin, though not necessarily in function, as the flippers of a seal and the hands of a human. 3. Immunology Relating to the correspondence between an antigen and the antibody produced in response to it. 4. Genetics Having the same morphology and linear sequence of gene loci as another chromosome. 5. Chemistry Belonging to or being a series of organic compounds each successive member of which differs from the preceding member by a constant increment, especially by an added CH<sub>2</sub> group. [From Greek *homologos*, agreeing: *homo-*, homo- + *logos*, word, proportion; see *leg-* in Appendix I.]

**homolographic** (*hōm'a-lō-grāf'ik*) *adj.* Maintaining the ratio of parts. [Greek *homalos*, even; see *sem-* in Appendix I + GRAPHIC.]

**homolographic projection** *n.* A map projection reproducing the ratios of areas as they exist on the earth's surface.

**homologue** also **homolog** (*hōm'a-lōg', -lōg', hōm'a-*) *n.* Something homologous; a homologous organ or part. [French, from



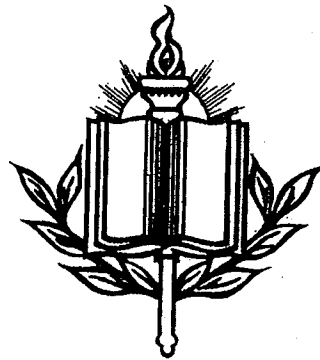
homocercal swordfish tail

a pat	oi boy
apay	ou out
Ar care	oo took
a father	oo boot
epel	u cut
e be	ur urge
i pit	th thin
i pie	th this
ipier	hw which
o pot	zh vision
o toe	a about item
o paw	♦ regionalism

Stress marks: (primary) (secondary), as in dictionary (dik'shə-nē-ē)

# EXHIBIT 8

# Webster's Encyclopedic Unabridged Dictionary of the English Language



*The dictionary entries are based on the First Edition of The Random House Dictionary of the English Language*

**PORTLAND HOUSE • NEW YORK**

**A-96**

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# E

**E**, **e** (ē), **n.**, pl. **E's** or **Es**, **e's** or **es**. 1. the fifth letter of the English alphabet, a vowel. 2. any spoken sound represented by the letter **E** or **e**, as in *met*, *meat*, *mere*, etc. 3. something having the shape of an **E**. 4. a written or printed representation of the letter **E** or **e**. 5. a device, as a printer's type, for reproducing the letter **E** or **e**. 6. U.S. a flag bearing the letter **E**, for *Efficiency*, presented during World War II as an award by the army or navy to factories meeting or surpassing their production schedules of war materials.

**E**, 1. east. 2. eastern. 3. English. 4. excellent. **E**, 1. the fifth in order or in a series. 2. (sometimes *i.c.*) (in some grading systems) a grade or mark, as in school or college, indicating the quality of a student's work or in need of improvement in order to be passing. 3. *Music*. a. the third tone in the scale of C major or the fifth tone in the relative minor scale. A minor. b. a string, key, or pipe tuned to this tone. c. a written or printed note representing this tone. d. (in the fixed system of solmization) the third tone of the scale of C major, called *mi*. e. the tonality having **E** as the tonic note. 4. (sometimes *i.c.*) the medieval Roman numeral for 250. Cf. *Roman numerals*. 5. *Physics*. *Elect.* electric field strength. 6. *Physics*. energy. 7. *Elect.* See *electromotive force*. 8. *Logic*. See *universal negative*. 9. a proportional shoe width size narrower than **EE** and wider than **D**.

**e**, *erg*. 1. *Math.* a transcendental constant equal to 2.7182818... used as the base of natural logarithms; the limit of the expression  $(1 + \frac{1}{n})^n$  as *n* approaches infinity. 2. *Logic*. See *universal negative*.

**e-**, var. of **ex-**, occurring in words of Latin origin before consonants other than *c*, *f*, *p*, *g*, *s*, and *t*. *emul*.

**E**, 1. Earl. 2. east. 3. eastern. 4. English.

**e**, 1. eldest. 2. Football. end. 3. entrance. 4. Baseball. error; errors.

**Ea** (ē/ā), **n.**, the Akkadian god of wisdom, the son of Anu and father of Marduk; the counterpart of Enki.

**-ea**, a formal element occurring in loan words from Latin, orig. in feminine adjectives; *cornea*, [*L* *-ea*, *-ae*, fem. of *-eus*, *-aeus*, *-eus*; see *-ean*]

**ea-**, each.

**E.A.**, educational age.

**E.A.A.**, Engineer in Aeronautics and Astronautics.

**each** (ēch), **adj.** 1. every one of two or more considered individually or one by one: *each stone in a building*; *a hallway with a door at each end*. —*pron.* 2. each one: *Each went his way*. —*adv.* 3. to, from, or for each; *apiece: They cost a dollar each*. [*ME* *ech*, OE *ēlc*, equiv. to *e* over (see *ē*) + (*ē*) *līc* (A) *like*; c. OHG *ēo-gilīh*, OFris *ēlīk*, D, LG *ēik*]

**Syn.** 1. **EACH**, **EVERY** are alike in having a distributive meaning. Of two or more members composing a (usually) definite aggregate, **EACH** directs attention to the separate members in turn: *Each child (of those considered and enumerated) received a large apple*. **EVERY** emphasizes the idea of inclusiveness or universality; it is also used of an indefinite number, all being regarded singly and separately: *Every child present received an apple* (no child was omitted). *Every child (of all in existence) likes to play*.

**Usage.** 2. Careful speakers make certain that **EACH**, which is a singular pronoun, is always used with a singular verb: *Each child has his own book*. *Each of the houses on this street is painted a different color*.

**each/other**, 1. each the other: *to love each other*. 2. one another (used as a compound reciprocal pronoun in oblique cases): *They struck at each other*. [*ME* *ech other*, OE *ēlc oðer*. See *EACH*, *OTHER*]

**ead-**, (in prescriptions) the same. [*L* *eādem*]

**Eadie** (ē/dē), **n.** a girl's given name.

**Eadmund I** (ēd'mənd). See *Edmund I*.

**Eadmund II**. See *Edmund II*.

**Eads** (ēdz), **n.** James Buchanan, 1820-87, U.S. engineer and inventor.

**Eadwine** (ēd'win), **n.** Edwin (def. 1).

**-eae**, plural of *-ea*: *tracheae*.

**ea-ger** (ē'gar), **adj.** 1. keen or ardent in desire or feeling; impatiently longing: *I am eager for news about them*.

**He is eager to sing**. 2. characterized by or revealing great earnestness: *an eager look*. 3. *Archaic*. keen; sharp; biting. [*ME* *egre* < OE *egre*, *agre* < *L* *acer* sharp] —*ea-gerly*, *adv.* —*ea-ger-ness*, **n.**

**Syn.** 1. fervent, zealous, enthusiastic.

**ea-ger** (ē'gar, ē'gar), **n.** Chiefly Brit. *eager*.

**ea-ger bea-ver** (ē'gar), **Informal**. a person who is excessively diligent or zealous, esp. one who appears to be currying favor or seeking advancement: *He would be popular in school if he weren't such an eager beaver*.

**ea-gle** (ē'gal), **n.**, *v.*, *glad*, *-gling*. —**n.** 1. any of several large, diurnal, accipitrine birds of prey, noted for their size, strength, and powers of flight and vision. Cf. *bald eagle*, *golden eagle*. 2. a figure or representation of an eagle, much used as an emblem: *the Roman eagle*. 3. a standard, seal, or the like bearing such a figure. 4. one of a pair of silver insignia in the shape of eagles with outstretched wings worn by a colonel in the U.S. Army, Air Force, and Marine Corps and by a captain in the U.S. Navy. 5. a lectern having the form of an eagle. 6. a gold coin of the U.S., issued until 1933, equal to 10 dollars, having on its reverse the figure of an eagle. 7. U.S. a. a representation in green of an eagle, used on playing cards to designate a suit in the pack additional to the four standard suits. b. a card of a suit so designated. c. eagles, the suit itself. 8. (*cap.*) *Astron.* the constellation Aquila. 9. *Golf*, a score of two below par on any hole. —*v.* 10. *Golf*, to make an eagle on (a hole). [*ME* *agle* < OE *agle*, *agle* < OPr *agila* < *L* *aquila* n. use of fem. of *aquilus* dark-colored]

**ea-gle boat**, a small antisubmarine warship.

**ea-gle eye**, 1. unusually sharp visual powers; keen ability to watch or observe. 2. a person who has sharp vision or who maintains a keen watchfulness.

**ea-gle-eyed** (ē'gal id'), **adj.** sharp-sighted.

**Eagle Grove**, a town in central Iowa. 4381 (1960).

**Eagle Lake**, a town in S Texas. 3585 (1960).

**ea-gle owl**, any of several large owls of the genus *Bubo*, having prominent tufts of feathers on each side of the head, esp. *B. bubo*, of Europe and Asia.

**Eagle Pass**, a city in S Texas, on the Rio Grande. 12,094 (1960).

**ea-gle ray**, of several rays of the family *Myliobatidae*, found in tropical seas and noted for the soaring movements by which they propel themselves through the water.

**ea-gle scout**, a boy scout who has earned 21 merit badges.

**ea-gle-stone** (ē'gal stōn'), **n.** a concretionary lump of ironstone about the size of a small egg, formerly believed to be carried by eagles to their nests as a magical aid in laying eggs. [*EA* *gle* < *stone*]

**ea-glet** (ē'glit), **n.** a young eagle. [*< F* *aiglette*. See *EAGLE*, *-et*]

**Eagle-ton Vil-lage** (ē'gal ten), a town in E Tennessee. 5068 (1960).

**ea-gle-wood** (ē'gal wōd'), **n.** *agaloch*. [trans. of Pg *páo d'águla* wood of *agaloch*, by confusion of Pg *águla* eagle with *águla* < Malayalam *agil* *agaloch*]

**ea-gre** (ē'gar, ē'gar), **n.** Chiefly Brit. a tidal bore or flood. Also, *eager*. [*earlier eager, eager*, equiv. to OE *ea* river + *gār* storm]

**Eaker** (ē'kar), **n.** Ira Clarence, born 1896, U.S. Air Force general.

**Ea-kins** (ē'kinz), **n.** Thomas, 1844-1916, U.S. painter.

**ea-dor-man** (ēd'dor mən), **n.**, pl. *-men*. Obs. *alderman*. Also, *ea/der-man*.

**Ea-ling** (ē'ling), **n.** a city in SE England, part of Greater London. 183,151 (1961).

**EAM**, National Liberation Front, a Greek underground resistance movement of World War II and political coalition of various leftist groups. [*< ModGk* *E* (*thniko*) (*A*) (*pentherotiko*) (*M*) (*elipo*)]

**-ean**, an element used to form adjectives from nouns with stems in *-ea*: *trachean*. [*< L* *-ēus* (Gk *-eios*, *-aeus*) (Gk *-atos*, *-eus*) + *-an*]

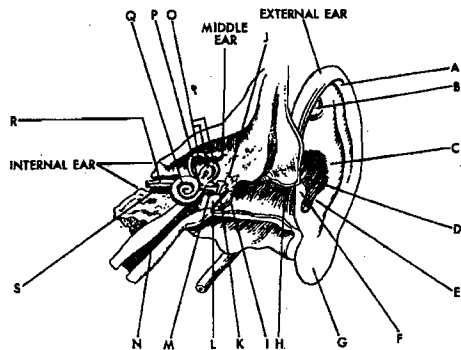
**E. & O.E.**, errors and omissions excepted.

**E. and P.**, extraordinary and plenipotentiary.

**ean-ling** (ēn'ling), **n.** Obs. a young lamb; kid. [*var. of* *YEANLING*]

**equal**, if, ice; hot, beer, order, oil, dock, dose, out; up, gallop, u as in circus; o as in button (but'n), fire (fīr),

**ear** (ēr), **n.** 1. the organ of hearing in man and other vertebrates, in man usually consisting of an expanded outer portion, the external ear, which receives sound vibrations that are passed into the middle ear, causing a vibration of its bones which in turn causes a movement of the fluid in the internal ear, the hair cells of which stimulate the auditory nerve which transmits the impulse to the brain. 2. the external part alone: *The*



Human ear (Transverse section)  
External ear: A, Helix; B, Fossa of antihelix; C, Antihelix; D, Concha; E, Antitragus; F, Tragus; G, Lobe; H, External auditory meatus. Middle ear: I, Tympanic membrane; J, Malleus; K, Incus; L, Tympanic cavity; M, Stapes; N, Eustachian tube. Internal ear: O, Semicircular canals; P, Vestibule; Q, Cochlea; R, Nerves; S, Internal auditory meatus

**teacher seized the student by the ear**. 3. the sense of hearing: *sounds that are pleasing to the ear*. 4. keen or sensitive perception of the differences of sound, esp. sensitiveness to the quality and correctness of musical sounds: *an ear for music*; *a violinist with a good ear*. 5. attention; heed: *to gain a person's ear*. 6. any part that resembles or suggests an ear in position or form, as the handle of a teacup. 7. *Archit.* crossette (def. 1). 8. *Journalism*. a small box in either upper corner of a newspaper page, usually the front page or split page, containing the name of or a symbol for the edition, a weather bulletin, a slogan, or the like. 9. *Furniture*. a, a decorative feature at the upper end of a leg. b. one of the decorative features at each end of a crest rail. 10. be all ears, to give all one's attention; listen: *She was all ears as the scandal was revealed*. 11. bend an ear, to listen attentively: *to bend an ear to a request for aid*. 12. bend one's ear, *Slang*, to talk to someone unimportantly and often so as to induce boredom: *Keep away from him because he'll bend your ear for hours if given the chance*. 13. by ear, without reference to, or dependence upon, written or printed music: *He sat down at the piano and gave a magnificent performance, playing completely by ear*. 14. fall on deaf ears, to be disregarded; pass unheeded: *Their pleas for an extension of time fell on deaf ears*. 15. give ear, to pay attention; listen carefully. Also, lend an ear. 16. go in one ear and out the other, to be heard but ignored; be put out of mind: *My repeated warnings to her went in one ear and out the other*. 17. have or keep one's ear to the ground, to keep well-informed about current trends; be shrewd or astute: *Because he had his ear to the ground, he made a large fortune in stock speculation*. 18. pin someone's ears back, *Slang*, to give a person a sound beating; defeat a person utterly: *If he doesn't behave himself I'll pin his ears back*. 19. set by the ears, to cause to dispute or quarrel: *His choice of a wife set his family by the ears*. 20. turn a deaf ear to, to refuse to listen to or consider (a request, petition, etc.): *He turns a deaf ear to requests for loans*. 21. up to one's ears, deeply involved or occupied: *We are up to our ears in work*. 22. wet behind the ears. See *Wet* (def. 12).